Comparative genomics of Sarcoptes scabiei provides new insights into adaptation to permanent parasitism and within-host species divergence

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Abstract

Background: Mites represent the second largest group with diverse niches and feeding habits, except for insects. Scabies mites are the causative agents of highly contagious skin disease in humans and more than 100 mammals. Although several versions of *Sarcoptes scabiei* genome have been published, i.e. var. *suis*, var. *canis* and var. *hominis*, the chromosome-level genome and population divergence is still desired for the community. Besides, the molecular mechanisms that scabies mites adapt to a parasitic lifestyle remains unclear. The taxonomy and ancestral origin of the scabies mite is unknown. **Results:** Here, we reported the first chromosome-level reference genome of *S. scabiei,* which was isolated from rabbits. The genome has a contig N50 size of 5.92 Mb, a total assembled length of 57.30 Mb, and ~12.65% of repetitive sequences and 9,333 protein-coding genes were predicted. Population genetics analysis supported that scabies mites isolated from different hosts can be subdivided by hosts, and humans are likely the primary hosts of scabies mites, followed by pigs, dogs, and rabbits. However, phylogeny results suggested that rabbit was infected with scabies long before they were domesticated by humans, contradicting previous hypothesis that humans transmitted scabies mites to animals through domestication. Comparative genomics between scabies mites and mites of other feeding habits provided clues concerning the mechanisms of adaptation to permanent parasitic life from morphology, detoxification, and metabolism. **Conclusions:** Together, the first chromosome-level *S. scabiei* genome and population genetics analysis indicated its genetic subdivisions and within-host species divergence, which also provide evidence for further control of this highly contagious skin disease.

Introduction

Mites (belonging to the Chelicerata, Arachnida, Acari) represent the most abundant group of species in the subphylum Chelicerata, with approximately 48,200 described species and an estimated total diversity up to 1 million species (Halliday *et al.* , 2000; Krantz, 2009). Their ecological niches and lifestyles are varied, such as the free-living house dust mites, plant-feeding spider mites, predatory mites, and parasitic mites. Among them, *Sarcoptes scabiei* represents a very rare species that has a unique permanent parasitic life in the epidermis of humans and mammals, including pets (dogs, cats), domestic animals (e.g., cattle, sheep, pig, horse, and rabbits, etc.), and more than 100 species of wild animals. *S. scabiei* causes scabies in humans or sarcoptic mange in animals, which is characterized by irritation, inflammation, hyperkeratosis, alopecia, pruritis, dermatitis, and lesions, and is generally accompanied by secondary infections (Arlian & Morgan, 2017; Escobar *et al.* , 2021; Pence & Ueckermann, 2002). Scabies has afflicted human societies for at least 2500 years (Orion *et al.* , 2006), and was also the first disease in the history of medicine with a definite

known cause (Friedman, 1934). Not only has scabies been listed among the top 50 most prevalent diseases and the top 15 most burdensome dermatological conditions worldwide, but also was officially designated as a neglected tropical diseases in 2017 (Hay *et al.* , 2014; Karimkhani *et al.* , 2017; WHO, 2017). A recent study showed that the human scabies disease burden was estimated as 204 million, with a prevalence ranging from 0.2% to 71.4% (Romani *et al.* , 2015). For animals, sarcoptic mange provokes distress, causing economic loss in the livestock industry, disease and death in wildlife (Fraser *et al.* , 2016). Therefore,*S. scabiei* is globally important for public health, pet health, animal husbandry production, and wildlife conservation.

As a permanent ectoparasitic mite, scabies mites have evolved from various levels. They have short and stubby legs to facilitate burrowing and crawling, legs III and IV of both sexes do not extend beyond the lateral-posterior margin of the idiosoma (Arlian & Morgan, 2017), while their relatives, such as surface-feeding mites *P. ovis* and *T. mercedesae* , as well as plant surface resident *T. urticae* , they use longer legs to secure themselves on the surface of their hosts. Moreover, using unique chewing mouthparts instead of piercing-sucking mouthparts make scabies mites more efficient in burrowing the skin, contributing to their highly contagious nature, and their activity in the epidermis induces extreme itching in the mammalian hosts. Compared with those mites whose niches and lifestyles are diverse, the potential parasitic mechanisms of *S. scabiei* in mammal skin are still poorly understood.

The *S. scabiei* species that parasitize various hosts are morphologically indistinguishable and have a 'high degree of host specificity and low degree of cross-infestivity'(Arlian *et al.* , 1984; Currier *et al.* , 2011; Fain, 1978); therefore, there is an ongoing debate regarding the taxonomy and origin of *S .scabiei* from different hosts (Alasaad *et al.* , 2011; Engelman *et al.* , 2013; Gakuya *et al.* , 2011; Matsuyama *et al.* , 2015; Pence & Ueckermann, 2002; Rasero *et al.* , 2010; Walton *et al.* , 1999). Although the taxonomy of *S. scabiei* from different hosts is uncertain, it is believed that a single, but variable, species that has evolved adaptations to infect a variety of mammals with limited cross-infestations between different hosts (Heukelbach & Feldmeier, 2006; Kraabl *et al.* , 2015), e.g.,*S. scabiei* var. *hominis* , var. *chimp* , var.*canis* , var. *suis* and so on (Matsuyama *et al.* , 2015; Walton *et al.* , 1999). However, the inconsistent use of gene loci across studies and conflicting results provided by limited gene markers cannot lead to the exact nature of the host specific adaptations, origin, and species differentiation (V Andriantsoanirina, Ariey, Izri, Bernigaud, Fang, Charrel*, et al.* , 2015; V Andriantsoanirina, Ariey, Izri, Bernigaud, Fang, Guillot*, et al.* , 2015; V. Andriantsoanirina *et al.* , 2016; Gakuya *et al.* , 2011; Mofiz *et al.* , 2016). To explain these questions, the high-quality genome assembly is essential. At present, although several versions of *S. scabiei* genome has been published, including var. *suis* , var. *canis* and var.*hominis* (Korhonen *et al.* , 2020; Mofiz *et al.* , 2016; Rider *et al.* , 2015), among which, Korhonen et al.(Korhonen *et al.* , 2020) reported a scaffold-level genome assembly of *S. scabiei,*the chromosome-level genome is still absent for the study of this highly contagious pathogen.

In this study, we employed a combination of sequencing methods, including Illumina pair-end sequencing, Pacific Biosciences (PacBio) single-molecule real-time (SMRT) sequencing, and chromosome interaction mapping (Hi-C) sequencing to get a chromosome-level genome of *S. scabiei* that isolated from rabbits. We also carried out whole-genome resequencing of 13 sarcoptic mite populations and downloaded 7 Illumina short read datasets from scabies mites distributed in four host species and three geographical locations to clarify the controversial taxonomic status and origin of *S. scabiei.* Comparative genomics study revealed the potential mechanism of the *S. scabiei* adaption to the parasitic life. These results will increase the awareness, education, and research into taxonomy, pathogenic biology, diagnosis, treatment, and prevention of scabies or sarcoptic mange.

Materials and Methods

Source of samples

The *S. scabiei* var. *cuniculi* was originated from a farm-collected New Zealand rabbit (Ya'an, China), and maintained in New Zealand rabbit, the strain has undergone sibmating to maximize homozygosity.

Twelve scabies mite colonies from three different mammal hosts (one from dog, three from pigs and eight from rabbits) were collected to perform re-sequencing (**Table S1)** . In addition, we also downloaded the

7 publicly available datasets from other representative *S. scabiei*populations to do further analysis (**Table S1)** , including one isolated from dogs, 2 isolated from humans and 4 isolated from pigs (Mofiz *et al.* , 2016; Rider *et al.* , 2015).

DNA preparation and genome sequencing

Adult mites, nymphs, larvae and eggs were collected in a 1.5 mL Eppendorf tube, treated with bleach solution to remove rabbit tissue and possible microbial contaminants and prepared for DNA extraction. Pool-staged mites were ground in a glass tissue grinder and DNA extraction was performed using Qiagen DNA purification kit (Qiagen, Valencia, CA, USA) according to manufacturer's protocol and the extracted DNA was qualified with Qubit 3.0 Fluorometer (Thermo Fisher Scientific, USA).

To obtain a high-quality scabies mite genome assembly, a combination of sequencing methods was used, including Illumina paired-end sequencing, Pacific Biosciences (PacBio) single-molecule real-time (SMRT) sequencing and chromosome interaction mapping (Hi-C) sequencing. In details, one short-insert (230 bp, paired-end) DNA library was constructed according to standard Illumina library prep protocols and sequenced on the Illumina HiSeq platform as 2 × 150 bp reads, which generated 4.7 Gb raw data. And then, a 20 kb PacBio long-reads library was constructed using the BluePippinTM Size-Selection System recommended by Pacific Biosciences and sequenced on the Pacbio sequel platform. A total of 16 Gb sequencing data was generated, including 1.4 million clean subreads with an average length of 12.065 kb and N50 value of 19.706 kb. Finally, to scaffold the genome, one Hi-C library was constructed from the purified DNA using the Illumina Mate Pair Sample Preparation Kit and sequenced using the Illumina HiSeq X platform, and 12.7 Gb was generated.

2.3 RNA preparation and sequencing

Total RNA was extracted from the tissues of pooled mites (adult mites, nymphs, larvae and eggs) using TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. RNA degradation and contamination were monitored by 1 % agarose gel electrophoresis. RNA purity was assessed using Nanodrop®2000 spectrophotometer (ThermoFisher Scientific, UK) and then quantified. RNA integrity was assessed using an RNA Nano 6000 Assay Kit with the Bioanalyzer 2100 system (Agilent Technologies, Santa Clara, CA, USA). RNA sequencing libraries were constructed using the NEB Next mRNA Library Prep Kit following the manufacturer's instructions and sequenced on the Illumina HiSeq X platform. Finally, a total of 25.03 Gb clean data were generated.

Genome assembly and evaluation of *S. scabiei* var.*cuniculi* genome

Jellyfish (v2.0) was used to estimate genome size based on k -mer (kmer=17) distribution using short-insert size libraries (Kingsford, 2011). The estimated genome size of *S. scabiei* var. *cuniculi* is 49.83 Mb and the heterozygous ratio is 1.02%.

Using long reads generated by the PacBio Sequel platform, contigs were assembled using the canu (canu-1.7) software (Koren *et al.* , 2017) with parameters setting as '-correct genomeSize=50m gnuplotTested=true stopOnReadQuality=false -pacbio-raw pacbio.fasta -trim genomeSize=50m gnuplotTested=true stopOnReadQuality=false -pacbio-corrected PacBio.correctedReads.fasta.gz -assemble genomeSize=50m gnuplotTested=true stopOnReadQuality=false -pacbio-corrected PacBio.trimmedReads.fasta.gz'. The initial assembly was then polished using Quiver (smrtlink 6.0.1) with default parameters (Chin *et al.* , 2013). Heterozygosity in the assembly was removed by Purge Haplotigs software (v1.0.4) (Roach *et al.* , 2018). Short Illumina reads were then used to correct any remaining errors by pilon (v1.22) with parameters set as follows: '-Xmx300G –diploid –threads 20' (Walker *et al.* , 2014). Finally, we used Hi-C data to scaffold *S. scabiei* var.*cuniculi* genome to chromosome-level by Lachesis software (version-201701) with default parameters (Burton *et al.* , 2013).

To evaluate the accuracy of the assembly at single base level, short Illumina reads were mapped to the *S. scabiei* var. *cuniculi*genome using BWA (H. Li & Durbin, 2009) with parameters setting as '-k 32 -w 10 -B 3 -O 11 -E 4' and performed variant calling with SAMtools (v1.8) (H. Li, 2011). Meanwhile, assembly completeness

was assessed based on Benchmarking Universal Single-Copy Orthologs (BUSCO v4.0, arthropoda_odb9) (Simao *et al.* , 2015) and Core Eukaryotic Genes Mapping Approach (CEGMA V2.5) (Parra *et al.* , 2007).

Genome annotation

Homologous comparison and *de novo* prediction methods were used to annotate the repeat sequences on *S. scabiei* var. *cuniculi*genome. RepeatMasker and the RepeatProteinMask v4.0.8 (https://www.girinst.org/repbase/) were performed for homologous comparison against Repbase database (*https://www.girinst.org/repbase/*) (Jurka *et al.* , 2005). For *ab initio* prediction, LTR_FINDER (http://tlife.fudan.edu.cn/ltr_finder/)(Xu & Wang, 2007), RepeatScout (http://www.repeatmasker.org/)(Price*et al.* , 2005) and RepeatModeler (v2.1) (http://www.repeatmasker.org/RepeatModeler.html) were first used for repetitive elements *de novo* candidate database constructing, and further annotated using RepeatMasker. Tandem repeat was predicted using TRF (http://tandem.bu.edu/trf/trf.html).

Gene prediction was performed through combination methods of homology-based prediction, *de novo* prediction and transcriptome-based prediction. For homologous annotation, protein sequences including *S. scabiei* var. *canis* ,*Metaseiulus occidentalis* , *Ixodes scapularis* ,*Tetranychus urticae* , *Drosophila melanogaster* ,*Tropilaelaps mercedesae* , *Pediculus humanus* ,*Tribolium castaneum* and *Stegodyphus mimosarum* were aligned against the *S. scabiei* var. *cuniculi* genome using TBLASTN (Altschul *et al.* , 1990). Blast hits that correspond to reference proteins were concatenated by Solar software (version 0.9.6) and low-quality records were filtered. Sequence of each reference protein was extended upstream and downstream by 1000 bp to represent a protein-coding region. GeneWise (Birney *et al.* , 2004) software was used to predict gene structure contained in each protein region. Homology predictions were denoted as "Homology-set". All RNA-seq clean data were first *de novo* assembled using Trinity (v2.0)(Grabherr *et al.* , 2011) and the assembled sequences were then aligned against the *S. scabiei*var. *cuniculi* genome using PASA pipeline v2.0.2(Haas *et al.* , 2003) with BLAT (Kent, 2002) as the aligner. Gene models created by PASA were denoted as PASA-T-set (PASA Trinity set). We simultaneously employed five tools of Augustus (Stanke & Morgenstern, 2005), GeneID (Guigo *et al.* , 1992), GeneScan (Burge & Karlin, 1997), GlimmerHMM (Majoros *et al.* , 2004), and SNAP(Korf, 2004) for *ab initio*prediction, in which Augustus, SNAP, and GlimmerHMM were trained by PASA-T-set gene models. In addition, RNA-seq reads were directly mapped to the genome using Tophat (v2.0.9) (Trapnell *et al.* , 2009), and then the mapped reads were assembled into gene models (Cufflinks-set) by Cufflinks (Trapnell *et al.* , 2010). According to these three approaches, all the gene models were finally integrated by EvidenceModeler(EVM v1.1.1)(Haas *et al.* , 2008). Weights for each type of evidence were set as follows: PASA-T-set > Homology-set > Cufflinks-set > Augustus > GeneID = SNAP = GlimmerHMM = GeneScan. In order to get the untranslated regions (UTRs) and alternative splicing information, PASA2 was used to update the gene structure. To achieve the functional annotation, the predicted protein sequences were aligned against public databases, including SwissProt (Bairoch & Apweiler, 2000), NR database (from NCBI), InterPro and KEGG pathway (Kanehisa & Goto, 2000) (release 76). Of that, InterproScan tool (Jones *et al.* , 2014) in coordination with InterPro database (Finn *et al.* , 2017) were applied to predict protein function based on the conserved protein domains and functional sites. NR, KEGG pathway and SwissProt database were mainly used to map gene set to identify the best match for each gene.

Reconstruction of phylogenetic relationship and estimation of divergence time

We retrieved the protein-coding sequence of 7 arthropod including*T. urticae* , *Apis mellifera* , *D. melanogaster* ,*I. scapularis* , *S. mimosarum* , *M. occidentalis* ,*T. mercedesae* and *a nematode Caenorhabditis elegans* from Ensembl (Release 85). For gene model with multiple alternative isoforms, only the longest transcript was selected to represent this gene. To identify orthologous genes, OrthoMCL pipeline with the parameter of "-inflation 1.5" (L. Li *et al.* , 2003) as used to construct gene families. In total, 15,542 gene families were identified, involved in 1,338 single-copy orthologous gene families.

The phylogenetic relationship of *S. scabiei* var. *cuniculi*was reconstructed using the 1,338 shared single-copy orthologous genes. The sequences were aligned by MUSCLE tool with default parameters (Edgar, 2004).

Sequences were then concatenated to one super-gene sequence for each species and formed a data matrix. The GTR-GAMMA was selected as the best substitution model deduced by jModeltest tool (Darriba*et al.* , 2012). Then the phylogenetic analysis was performed using maximum-likelihood (ML) algorithm in RAxML tool (Stamatakis, 2006). The best-scoring ML tree was inferred by rapid BP algorithm and ML searches after performing 1,000 rapid bootstraps. The MEGA (version 7) was used for visualizing the constructed phylogenetic tree (Kumar*et al.* , 2016).

Furthermore, divergence time between *S. scabiei* var.*cuniculi* and other species were estimated based on the phylogeny. Four calibration times obtained from TimeTree database were used to calibrate divergence dates of other nodes on this phylogenetic tree (Sudhir *et al.* , 2017). In this process, we implemented the Monte Carlo Markov Chain algorithm for divergence time estimation by MCMCtree tool in PAML package (Yang, 2007). Finally, we found that*S. scabiei* var. *cuniculi* was separated away from its closest species of *T. urticae* at approximate 338.8 million years ago.

Homolog annotation method was applied for gene models prediction of scabies mites variants (isolated from pigs and humans)(Mofiz *et al.* , 2016),*Psoroptes ovis* (Burgess *et al.* , 2018) and *Dermatophagoides pteronyssinus*(Waldron *et al.* , 2017) that only have genome assembly files available in public database. OrthoMCL pipeline was employed to acquire shared single copy genes, molecular phylogenetic relationship of scabies mites from four hosts with plant-living, free-living, predatory mites, and other parasitic mite species that have available genomic data sets was constructed based on shared single copy genes generated from the same methods mentioned above.

Gene-family evolution and identification of gene families related with detoxification

The evolutionary dynamics (expansion/contraction) of gene families were analyzed using CAFÉ tool(De Bie *et al.* , 2006) with a stochastic birth and death model. Global parameter λ was estimated based on the phylogenetic tree and the datasets of gene family clustering. Viterbi method in CAFÉ was employed to identify the significantly changed families (p -value < 0.05). Finally, significantly changed expansion/contraction gene families were used to perform enrichment analysis.

To further analyze gene families of detoxification enzymes and transporters, the *S. scabiei* var. *cuniculi* genome sequence assembly was searched by TBLASTN (E -value=10^{-5}) (Altschul *et al.* , 1990) with close arthropod relatives including *T. urticae* , *T. mercedesae* ,*M. occidentalis* , and *D. melanogaster* target gene family protein sequences. The Basic Local Alignment Search Tool (BLAST) hits were then conjoined by Solar software (Yu*et al.* , 2006). GeneWise was used to predict the exact gene structure of the corresponding genomic region on each BLAST hit (Birney *et al.* , 2004). We then annotated preliminary identified candidate genes with Pfam database (*http://pfam.xfam.org/*) and NR database to get putative gene sets. Finally, a The proteins of target genes were aligned with mafft software (Katoh & Standley, 2014) and a neighbor-joining tree was constructed with TreeBest (Vilella *et al.* , 2009) with aligned by MAFFT software (Katoh & Standley, 2014).

Characterization of Hox genes

We identified putative Homeobox genes in *S. scabiei* var.*cuniculi* genome sequence assembly by performing TBLASTN (E -value=10^{-5})(Altschul*et al.* , 1990), using curated Homeobox proteins from *A. mellifera, Bombyx mori, Anopheles gambiae, Daphnia pulex, D. melanogaster, I. scapularis, Pachycrepoideus vindemmiae, Strigamia maritima, T. urticae,* and *Tribolium castaneum* . The Basic Local Alignment Search Tool (BLAST) hits were then conjoined by Solar software (Yu *et al.* , 2006). GeneWise was used to predict the exact gene structure of the corresponding genomic region on each BLAST hit (Birney *et al.* , 2004). HMM searches of the above genes against the Pfam database (http://pfam.xfam.org/) revealed each to have PF00046.29 domain. The classification of deduced proteins and their integrity were verified using BlASTP with model species *D. melanogaster* Hox genes.E -values $< 10^{-5}$ was considered as significant hits of similarity.

Phylogenetic and population genetic analysis

Twelve scabies mite colonies from three different mammal hosts (one from dog, three from pigs and eight

from rabbits) were sequenced on the Illumina HiSeq X sequencing platform using standard procedures. In addition, we also downloaded 7 individuals in the public database from other representative populations, including one mite population isolated from dogs, 2 isolated from humans and 4 isolated from pigs (Mofiz *et al.* , 2016; Rider *et al.* , 2015). Detailed information for all 20 samples was shown in **Tables S1** . Consequently, a total of 136.45 Gb high-quality paired-end DNA sequence was obtained. For downloaded datasets, high sequencing depth data were truncated to around 50x coverage for further analysis.

FASTQC (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/) was used for reads quality control. Clean reads were then aligned to the*S. scabiei* var. *cuniculi* genome using Burrows-Wheeler Alignment MEM (BWA-MEM) version 0.7.8 with default parameters except for the "-t 4 -k 32 -M -R" option (H. Li & Durbin, 2009). The 'sort' and 'rmdup' commands of SAMtools (v1.3) were used to perform data manipulation and alignment statistics. SNP calling was performed by SAMtools (v1.3) 'mpileup' command (H. Li *et al.* , 2009), bcftools 'call' command. To estimate individual admixture assuming different numbers of clusters, the genetic structure was inferred using sNMF (*http://membres-timc.imag.fr/Olivier.Francois/snmf/software.htm)* , which is based on sparse non-negative matrix factorization algorithms. We calculated the numbers of genetic clusters from 2 to 7 to explore the convergence of individuals with default settings and plotted $K$from 2-4.

The software GCTA (*http://cnsgenomics.com/software/gcta/*) was used for principal component analysis (PCA) with biallelic SNPs of the 20 individuals. Only the first two significant components were plotted. The pam function of Rggfortify package (*https://cran.r-project.org/web/packages/ggfortify/index.html*) was used to determine the significant level of the principal components.

2.10 Demographic history reconstruction

To reconstruct the demographic history for 20 scabies mite populations, we applied the pairwise sequentially Markovian coalescence (PSMC) model to evaluate the long-term changes in effective population size (H. Li & Durbin, 2011). To ensure the consensus sequence quality, all 20 samples with high sequencing depth were used for each geographic region. Bases of low sequencing depth (a third of the lowest depth) or high depth (three times of the highest depth) were masked. The required input format files were converted from consensus sequence by the utility fq2psmcfa provided by the PSMC software. The parameters were set as follows: -N30 -t15 -r5 -p 4+25*2+4+6. The generation time (g) was 0.0575 year per generation (21 days) and the mutation rate (u) is 8.4 x 10^{-9} per site per generation.

2.11 Selection signature analysis

Two complementary approaches based on the allele frequencies of variable sites were used to identify regions potentially affected by long-term selection. We calculated population fixation statistics (FST) and nucleotide diversity ($\vartheta\pi$) for each sliding window in 10-kb windows with 5-kb step size. We Z-transformed the distribution of FST and calculated the log value of $\vartheta\pi$ ratios. Top 5% of log-odds ratios for both $\vartheta\pi$ and FST were chosen as putative selection targets.

Results

3.1 A high-quality, chromosome-scale *S. scabiei* reference genome

A total of 33.4 Gb of sequence data (670.28-fold genome coverage based on an estimated genome size of 49.83Mb) was generated (**Table S2; Figure S1)** . We obtained a high-quality chromosome-scale reference genome of *S* . *scabiei* var. *cuniculi* , with contig N50 size of 5.92 Mb and total assembled length of 57.30 Mb (**Table 1**), of which 100% was anchored to nine chromosomes (**Figure 1; Table S3**). The high accuracy and completeness was represented by the normal GC content (33.23% of genome) (**Figure S2**), the mapping rate of 97.27% of short sequencing reads, 0.001472% of homozygous SNPs (**Table S4**), and the 97.98% and 89.0% of genome completeness assessed by the Core Eukaryotic Genes Mapping Approach (CEGMA)(Parra *et al.* , 2007) and Benchmarking Universal Single-Copy orthologues (BUSCOs) (Simao *et al.* , 2015) strategies (**Tables S5-6**).

Genome-wide searching and homology prediction results showed 12.65% of the scabies mite genome belongs to

transposable element (TE) families (7,247,159 bp, **Figure S3; Tables S7–8**). We annotated the genes using combination methods of homology searching, *ab initio*prediction, and direct mRNA sequencing evidence. In total, 9,333 protein-coding genes were identified (**Table S9; Figure S4**), and approximately 99.30% of these genes were functional annotated either in Kyoto Encyclopedia of Genes and genomes (KEGG) pathway database (Kanehisa & Goto, 2000), InterPro (Mulder *et al.* , 2007) and Gene Ontology (GO) (Ashburner, 2000) (**Table S10**).

3.2 Evolution of the scabies mite genome

To determine the evolution of the scabies mite genome in the context of the Chelicerata, we collected seven other arthropods and a nematode as outgroup for phylogeny analysis. A total of 15,542 gene families and 1,338 shared high confidence single-copy orthologous genes (**Figure S5**) were identified. The phylogenetic tree resulted in a well-supported phylogeny (**Figure 2a**): scabies mite and spider mite clustered together (Acariformes), while *Tropilaelaps* mite, predatory mite, and black-legged tick clustered together (Parasitiformes) and formed a separate group with *Stegodyphus mimosarum.* Based on this phylogenetic tree, we estimated that *S. scabiei* and *Tetranychus urticae* separated at approximately 338.8 Mya (**Figure 2a**), which indicated a relatively distant relationship between these two species. To further understand the phylogenetic relationship of scabies mites from various hosts, we used protein-coding single-copy orthologous genes of scabies mites from four hosts, as well as free-living mite *Dermatophagoides pteronyssinus and* parasitic mite *Psoroptes ovis* . This result showed that*S. scabiei* isolated from rabbits is genetically similar to*S. scabiei* isolated from humans, and then with pigs and dogs, followed by the free-living dust mite and the surface living scab mite, but distantly related to the spider mite (*T. urticae*) (**Figure 2b**). The phylogeny structure supported the previous study that the subclass Acari is diphyletic, with the superorders Acariformes (scabies mite and spider mite) and Parasitiformes (*Tropilaelaps* mite and predatory mite) being distantly related (Gu *et al.* , 2014; Hoy *et al.* , 2016). As only colonies from one individual animal and one geographical location were used for one host species, whether scabies mites from individual animals have any intrinsic relationship remains unknown. Thus, we are wondering that the so called "variants" more reasonable to be classified by host species or geographical locations?

To answer these questions, we expanded the sample size to 20 including four host species (humans, dogs, pigs and rabbits) and three geographical locations (China, Australia and America) (**Table S1; Figure S6**). Genome alignment indicated a mapping rate of 82.74–98.09% and ˜40-fold depth for each individual relative to our rabbit mite reference genome (**Table S11)** . After single nucleotide polymorphism (SNP) calling (**Table S12**), we examined the correlation between host species and geographical locations. The results showed that, although extremely similar genetic diversities were observed among these populations, both principal components analysis (PCA) consistently supported four distinct groups according to the host species (**Figure 2c**). Specifically, rabbit mites seem to be relatively distinct with mites from other three host species. Varying the number of presumed ancestral populations (K) from two to four, we found that rabbit mites remain distinct with mites from other three hosts (**Figure S7**). Interestingly, mites from humans and dogs cluster together, which may reflect the intimate relationship of these two hosts and indicated potential transmission between each other.

Although no direct evidence reported, the current scientific community believed that humans are the primary host of scabies mites, and other animals get infected from humans during the domestication (Currier *et al.* , 2011). To provide clues for the origin and transmission of scabies mites, PSMC was used and the results revealed a varied demographic history from over 100 kyr (1,000 years) to 10 kyr ago (**Figure 2d**), a period significantly younger than any of the currently reported fossil mites, including a nearly modern looking fossil oribatid mite (order Acariformes) that existed in the Devonian (late Paleozoic) period at ˜380 mya (million years ago)(Norton *et al.* , 1988), and the earliest fossil Astigmata mites at ˜28 mya (Petrunkevitch & Alexander, 1952). For human mites, the origin time is around 100 kyr ago (**Figure 2d**), nearly the same time with the emerging of the modern humans (Fenner, 2010; Hu *et al.* , 2017), supporting that humans are the primary host of scabies mites (Currier *et al.* , 2011b). However, for mites from other hosts, the origin time of these mites is far earlier than their hosts were domesticated by humans. To be specific, pigs, dogs,

and rabbits became infected with mites at around 100 kyr, 61 kyr, and 45 kyr ago, while these hosts were domesticated at around 10 kyr, 15 kyr, and 1.5 kyr ago (**Figure 2d; Table S13**). We also noticed that the effective population size of rabbit mites is significantly larger than mites from any of the other three hosts, which may reflect the parasite load of these hosts.

3.3 Specialized morphology to adapt an obligate parasitic life

The skin of mammalian species is composed of epidermis, dermis and hypodermis (**Figure 3a**). As a permanent parasitic mite species, scabies mites burrow into the epidermis of the skin, and resident at the interface of stratum lucidum and stratum granulosum (**Figure3b**). Belonging to a member of chelicerate, the adult scabies mite body plan comprises the anterior prosoma bearing the chelicerae, pedipalps, and the four pairs of walking legs, and the posterior opisthosoma (**Figure 3c**). After long time of adaptation, the four walking legs of scabies mites has become extremely stubby to adapted to its parasitic environment in the epidermis, while for other mites such as surface living and free-living mites, the length of walking legs remains long (**Figure 3c**). Interestingly, when we observed the morphology of species in class Acari, we found that for species in the superorder Acariformes, the anterior and posterior two pairs of legs were distantly distributed and the proportion of the abdominal segments were reduced, while for species in the superorder Parasitiformes and the velvet spider, all the legs were very close to each other and the abdominal segment is relatively longer (except*Metaseiulus occidentalis* , which seems a transactional species) (**Figure 3c; Figure 3d, left panel**). Therefore, we analyzed the structurally and functionally conserved Hox genes of these related species, including *lab* , *pb* , *Hox3/Zen* , *Dfd* ,*Scr* , *ftz* , *Antp* , *Ubx* , *Abd-A* , and*Abd-B* , hoping to find potential clues to explain this phenomenon. The results showed that *S. scabiei* has eight of ten canonical Hox genes that are present in the arthropod ancestor, except Z*en* and*Abd-A* , and no gene duplication events (**Table S14**). The loss of Z*en* and *Abd-A* seems common and unique for species in superorder Acariformes (**Figure 3d, central and right panel**).

3.4 Specialized metabolism to adapt an obligate parasitic life

The scabies mite burrows into the skin of its host, and then resides in the lower epidermis close to the dermis, using host skin and intracellular fluid (lymph) that seeps into the burrow as food (Estes *et al.* , 1983; Neste & Lachapelle, 1981; Van Neste, 1984). Compared with the other eight species genes in specific families to *S. scabiei* were significantly enriched in protein metabolic-related GO categories, especially in proteolysis, serine-type peptidase activity, serine-type endopeptidase activity, cysteine-type peptidase activity, peptidase activity, and endopeptidase activity (**Figure 4**). KEGG analysis results showed categories associated with the digestive system (Protein digestion and absorption, and Pancreatic secretion), lipid metabolism (Fatty acid metabolism, and Biosynthesis of unsaturated fatty acids), transport and catabolism (Lysosome) and cell growth and death (Apoptosis) (**Figure 4**) were also highly enriched. These results reflected that *S. scabiei* var. *cuniculi* may underwent natural selection pressure by living in mammalian skin, evolved to have better ability of digesting proteins to break through the skin barrier and migrate in the epidermis, and most importantly, to meet the requirement of nutrition.

Besides, genes in the families that were shared only by ectoparasite scabies mite and *Tropilaelaps* mite are highly enriched in the biological process of cellular nitrogen compound metabolic process and nitrogen compound metabolic process (**Figure S8-S9**), probably related to carnivorous diets of both scabies mite and*Tropilaelaps* mite. These genes were also enriched in KEGG pathway of human diseases, such as Alzheimer's disease, Arrhythmogenic right ventricular cardiomyopathy (ARVC), Dilated cardiomyopathy, and Cardiac muscle contraction (**Figure S8; Table S15**). We speculated that the enhancement of heart muscle-like function is an adaption of the aerobic nature of scabies mites in the hypoxic skin environment (Arlian *et al.* , 1988).

Scabies mites have been known to well adapted to live in the epidermis of the skin, protecting them from the environment. According to expansion and contraction analysis, three gene families were expanded, and 34 gene families were contacted. The primary contributor to the acquisition of new functions and physiology is gene duplication (Nasvall *et al.* , 2012). The three expanded gene families including the vitamin D-binding

protein (46 genes), synaptotagmin (12 genes) and HAUS complex (7 genes). The vitamin D-binding protein is the major binding/transport protein for all vitamin D metabolites (Bouillon *et al.* , 2020), genes in synaptotagmin family encode proteins that regulate calcium-dependent membrane fusion events (Wolfes & Dean, 2020), both were associated with enhanced absorption ability of nutrients. Among the 34 contracted gene families in scabies mites, genes were over-represented in the process of materials transport **(Tables S16-17**). We discovered four gene families that implicated in digestion, detoxification and transport of xenobiotics, including cytochrome P450 (CYP), carboxyl/cholinesterases (CCE), glutathione-S-transferase genes and ATP-binding cassette transporter C group and found unique scabies mite composition (**Tables 2-3; Table S19-S20)** . A total of only 25 cytochrome P450 (CYP) genes in *Sarcoptes scabiei* , followed by*Pediculus humanus* (36 genes), *T. mercedesae* (42 genes), and *Apis mellifera* (46 genes) (**Table 2**); of which the number of genes in *CYP4* clan being close to the number of counterparts in *A. mellifera* (4 genes), but far less than the number found in other mites (16˜23 genes); members of CYP2 clan (three genes) and Mito clan (three genes) have orthologs in*Drosophila melanogaster* (**Figure S10**), indicating that scabies mites only retain the genes that support basic life. A notable contraction is also found in the family of carboxyl/cholinesterases (CCE) that include 11 genes compared with other three mites (31-69 genes), and 6 genes in subclass acetylcholinesterase (AChEs) compared with 22–59 genes in other mites (**Table 3**). Although the total number of ABC transporters remain the same, we discovered 14 multidrug resistance proteins that belong to the ATP-binding cassette (ABC) transporters (class C), while other mites have 20–39 genes (**Table S18 and Figure S11**). Finally, scabies mites have 13 glutathione-S -transferase genes (**Table S19 and Figure S12**) that can be assigned to four subfamilies: Delta/Epsilon (4 genes), Mu (6 genes), Zeta (1 gene), and Kappa (2 genes), interestingly, both mu and kappa appear to be tandem repeats in the genome. The relatively small number of P450 genes in honey bee was thought to be a consequence of the social organization of beehive, which shields the queen and larvae from environmental exposure to toxins (Claudianos *et al.* , 2006). It is likely that the extremely contracted detoxification genes in scabies mites might be the consequences of long time living in the epidermis of the skin, protect mites from environmental exposure to toxins.

3.5 Strong selective sweep signals provided clues to the genetic basis of variant divergence and cross-infestivity

Scanning electron microscopy and light microscopy showed that *S. scabiei* lives in the skin stratum corneum reside at the interface of stratum lucidum and stratum granulosum (Estes *et al.* , 1983; Neste & Lachapelle, 1981; Van Neste, 1984). As shown in**Table S20** , the epidermis of humans, pigs, dogs and rabbits are 46.9 ± 2.3 μm, 65.8 ± 1.8 μm, 18.94 ± 2.29 μm, and 17.0 ± 1.2 μm thick, respectively (Bhandal *et al.* , 2012; Bronaugh *et al.* , 1982; Nicoli *et al.* , 2008), while the stratum corneum of them are 16.8±0.7 μm, 26.4±0.4 μm, NA and 11.7±0.5 μm. According to the results of PSMC, humans, pigs, dogs and rabbits get infected with scabies mites for more than 30 kyr ago, to reveal the potential genome footprint that may left by a couple of hundred thousand years co-evolution of the scabies mites and the hosts, we used FST & $\vartheta\pi$ to find possible selection sweeping signal between any of the two hosts. As shown in **Figure 5,** strong selective signals were observed between pig mites and human mites: about 10 times as many genomic regions with strong selective sweep signals in pig mites (3.84% of the genome, containing 358 genes) as there are in human mites (0.40% of the genome, containing 37 genes), with significant enrichment in "cysteine-type peptidase activity (10 genes), Neuroactive ligand-receptor interaction (18 genes), and Apoptosis (11 genes) (**Table S21**).There are three times as many genomic regions with strong selective sweep signals in dog mites (0.81% of the genome, containing 77 genes) as there are in human mites (0.27% of the genome, containing 25 genes), with high enrichment in "cysteine-type peptidase activity (five genes) and apoptosis (five genes)(**Table S21**). As shown in **Table S22-24** , the involved genes mainly including Sar s 1 allergen SMIPP-C (Peptidase C1A, papain C-terminal) and group 3 allergen SMIPP-S (Peptidase S1). However, as a recently emerging mite variant, rabbit scabies mites showed very limited selective sweeping signals compared with mites from any of the other three hosts (**Table S21**), especially with human mites and dog mites, which might be the explanation of cross-infestivity between rabbits and the other three hosts.

Discussion

Genome assembly and evolution

Scabies mites represent a highly contagious ectoparasite that can affect more than 100 mammal species (Escobar*et al.* , 2021). In this study, we presented the chromosome-scale genome assembly for ectoparasite *S. scabiei* . To the best of our knowledge, this is the first chromosome-level genome of all mite species to be determined to date (**Table 1**), providing a reference genome for comparative genomics of mite biology and further study of scabies mite.

Genome evolution results showed that scabies mites from four hosts clustering together, and rabbit mite is closer to human mites followed by pig mites and dog mites. However, the population genetics results indicated the clear cluster was defined by hosts, and rabbit mites seems distantly related with other mites, providing evidence supporting the hypothesis that *S. scabiei* is not a single panmictic population and genetic subdivisions occurs according to the hosts (Alasaad *et al.* , 2011; Walton *et al.* , 2004). It thus can be concluded that *S. scabiei* from various hosts are genetically similar to each other and are likely variants of one species that mainly clustered by host species.

If the variants classified by hosts is the case, is there any order of infection time for mites from these hosts? Surprisingly, the origin time of human mites support the current scientific consensus that humans are the principal host for Sarcoptes mites. Domestication of dogs can be traced back to at least around 15,000 years, and possibly earlier, being domesticated from the gray wolf in East Asia around 100,000 years ago (Bardeleben *et al.* , 2005; Currier *et al.* , 2011; Savolainen *et al.* , 2002; Wayne *et al.* , 1997); moreover, recent studies have shown that, in southern East Asia, the groups of dogs and wolves began to diverge about 33,000 years ago (Skoglund *et al.* , 2015; Wang *et al.* , 2016; Wang *et al.* , 2013). The estimated origin time of dogs (about 37 kyr - 61 kyr) all fall within the time frame of human domestication of domestic dogs (15,000 years to 100,000 years ago), indicating that the canine-derived scabies mites may have come from human-derived scabies mites. However, the results showed that pigs and rabbits get infected with scabies mites long before they were domesticated by humans, contradicting the hypothesis that humans transmitted scabies mites to animals through domestication activity (Currier *et al.* , 2011a; Friedman, 1936). The possible transfer of human-derived mites to dogs probably reflected the intimate relationship of humans and dogs.

4.2 Genetic basis of scabies mites to adapt an obligate and permanent parasitic life

As a permanent ectoparasitic mite, scabies mites have evolved from various levels. When we analyzed the mechanism that influenced morphology of the species in Acari, we found the Hox gene family divergence may cause the differences of body plan in superorder Acariformes and Parasiformes, especially the absence of Z*en* and*Abd-A* . For Chelicerate species like spiders and mites, Z*en*and *Abd-A* were reported to function in body plan of the prosoma and the opisthosoma (Hughes & Kaufman, 2002). Previous study showed that, the function of *Zen* has transferred from a Hox-like role to a role in the extraembryonic tissues due to the functional overlap with other Hox proteins (Hughes & Kaufman, 2002; Pick, 2016), thus pretended to be lost for species in the Acariformes that generally have small genomes (**Table S25)** . The expression of *Abd-A* and *Abd-B*reflects the differences in the insect abdomen, and *Abd -B*acts to suppress *Abd-A* in posterior segments, and suppresses posterior segmentation (Celniker *et al.* , 1989; Jordi *et al.* , 1986; Karch *et al.* , 1990). Previous data supportted a model that inversion of the *Abd-B* locus results in the loss of *Abd-A* , and correlated with reduced trunk segmentation (Pace *et al.* , 2016), and in this study, the Hox clusters and transcription direction in *S. scabiei* , *P. ovis* and *T. urticae* implicated the same mechanisms for the trunk segmentation of species in Acariforms. These results indicated that the morphological evolution correlated with the loss of specific Hox genes.

Genes in families specific to scabies mainly enriched in nutrition absorption and digestion of proteins and lipids. And genes in families of cytochrome P450 (CYP), carboxyl/cholinesterases (CCE), and multidrug resistance proteins of the ATP-binding cassette transporter C group are strikingly contracted, and members in these families were reported to function in a wide range of detoxification events (Dermauw *et al.* , 2013; Enayati *et al.* , 2005; X. Li *et al.* , 2007). Scabies mite lives in the epidermis of the mammal skin, which

is a relatively enclosed stable environment. Compared with *P. humanus* and *T. mercedesae* that live on the surface of the hosts, scabies mites have limited chances of encountering toxicants than other ectoparasites, thus the strikingly contracted gene families that are of important in metabolizing toxic xenobiotics in insects and the acquisition of insecticide resistance indicated a less effective detoxification system and an adaption to the enclosed environment.

Genetic basis of variant divergence and cross-infestivity

To date, there is no well-accepted standard to define subspecies or variants of mites, especially by using limited gene markers. In this study, we considered mites from different hosts as variants based on results of PCA and phylogenetic analysis. Although there is no direct evidence of host shift, comparative genomics analysis may provide clues for the cross-infectivity of these mites. It is known that *S. scabiei* reside at the interface of stratum lucidum and stratum granulosum (Estes *et al.* , 1983; Neste & Lachapelle, 1981; Van Neste, 1984), and mites have to burrow deep through stratum corneum to get to their destination, therefore, the thickness of stratum corneum may partly reflected the difficulties of mites to break through the barriers of the skin.

The selection signal between human mites/pig mites, human mite/dog mites quantitatively reflected the adaption to the new host in shaping the genome. Genes enriched in "cysteine-type peptidase activity" and "apoptosis" mainly encode Sar s1 allergen scabies mite inactive cysteine proteases (SMIPP-Cs). The function of these proteins is promoting blood coagulation and changing the structure and density of fibrin clots, making them resistant to fibrinolysis, thus protecting scabies mites from the host immune system (Fernando *et al.* , 2021). These functions were thought to contribute to parasitic lifestyle. Neuroactive ligand-receptor interaction (18 genes) is a function of environmental information processing (**Table S28**). Most of the group 3 allergen SMIPP-S genes occur in tandem, studies have shown that these proteins might function by binding and protecting target substrates from cleavage by host immune proteases, thus preventing the host from mounting an effective immune challenge (Fischer *et al.* , 2009). Besides, the presence of receptors, such as the olfactory receptor, rhodopsin-like G protein-coupled receptor, and the 5-hydroxytryptamine receptor family, suggested that scabies mites in omnivorous pigs have evolved to have a better ability to process environmental information, and thus adapted to a more complicated pig skin environment.

A previous study reported that mites from scabies-infected dogs can establish permanent infections on domestic rabbits and these mites can then re-infect dogs (Nicoli *et al.* , 2008). Interestingly, it is reported that the human and the pig stratum corneum share very similar lipid types and percentage of lipids (Hammond *et al.* , 2000), which suggested the possibility of the transmission of scabies mites from humans to dogs. Compared with the other three hosts, rabbits have the shortest generation time (**Table S13**) and are more susceptible to scabies mites. According to the statement of local farm workers, we also learned that humans who come in contact with rabbit mites experience intensive itching symptoms; however, because humans generally apply drugs before the mites settle down on the skin, we do not know if rabbit mites can establish a permanent infection on humans or vice versa. The condition of pigs living with rabbits is very rare, thus few reports have been published about the cross-infestivity between pig mites and rabbit mite. The results of the pairwise selective sweeping analysis provided clues to investigate cross-infestivity. Except in humans, it is feasible to investigate the genetic basis of cross-infestivity by performing artificial infection experiments to test cross-infestivity and differentially expressed genes during host shift.

Conclusions

In this study, a chromosome-scale genome assembly was reported for *S. scabiei* , a highly contagious ectoparasite that can affect more than 100 mammal species. Comparative genome analysis illustrated the possible mechanisms of scabies mites adapted to a permanent parasitic life, including metabolism, morphology and detoxification. Whole genome re-sequencing analysis showed that scabies mites cluster by host species rather than geographical location, and analysis of their demographic history supported the view new insights that humans were the primary hosts of scabies mites, followed by pigs, dogs, and rabbits, but was inconsistent

with the previous hypothesis that humans transmitted scabies mite according to the domestication time of these hosts. As the first chromosome-scale genome of mites, *S.scabiei* genome and comparative genomics study will provide solid foundation to promote the study of mites phylogeny and biology, especially for the study of control strategy for scabies and other mites.

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Conflict of Interest

The authors declare no competing interests.

Ethical Statement

The animal study was reviewed and approved by the Animal Care and Use Committee of Sichuan Agricultural University (SYXK2019-187). All animal procedures used in this study were carried out in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, Bethesda, MD, USA) and recommendations of the ARRIVE guidelines (https://www.nc3rs.org.uk/arrive-guidelines).

Supplementary information

Supplemental information has been submitted as supplemental material.

Authors' contributions

Conceptualization, G.Y.Y., J.X.; Data curation, Q.H.W., S.W., S.Y.W.; Formal analysis, J.X., Q.H.W., S.Y.W.; Funding acquisition, G.Y., S.Y.W.; Investigation, W.H., X.G., R.H., X.P.; Methodology, J.X., Q.H.W., S.W.; Project administration, G.Y.Y., J.X.; Resources, G.Y.Y, J.X.; Software, Q.W., S.W.; Supervision, G.Y.Y., J.X.; Validation, Q.H.W., S.Y.W., S.W.; Visualization, J.X., S.Y.W., Q.H.W.; Writing–original draft, J.X.; Writing–review & editing, G.Y.Y., J.X., Q.H.W., S.W., S.Y.W., W.H., Y.X., X.B.G., R.H., X.R.P.. All authors contributed to the writing and review of the final manuscript, with G.Y., J.X., S.Y.W., Q.H.W., and S.W. playing the key roles. All authors read and approved the final manuscript.

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Availability of data and materials

All raw data for the genome sequencing, RNA-seq and whole genome re-sequencing in this study have been deposited into the GenBank Sequence Read Archive (SRA) database with the BioProject accession PRJNA749654, the BioSample accession SAMN20424381 to SAMN20424399, and the accession for raw data from SRR15371646 to SRR15371664. The genome assembly and annotation information are available in figshare through*https://doi.org/10.6084/m9.figshare.16999372.v1.*The genome assembly is also available in NCBI under accession GCA_020844145.1.

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Figure legends

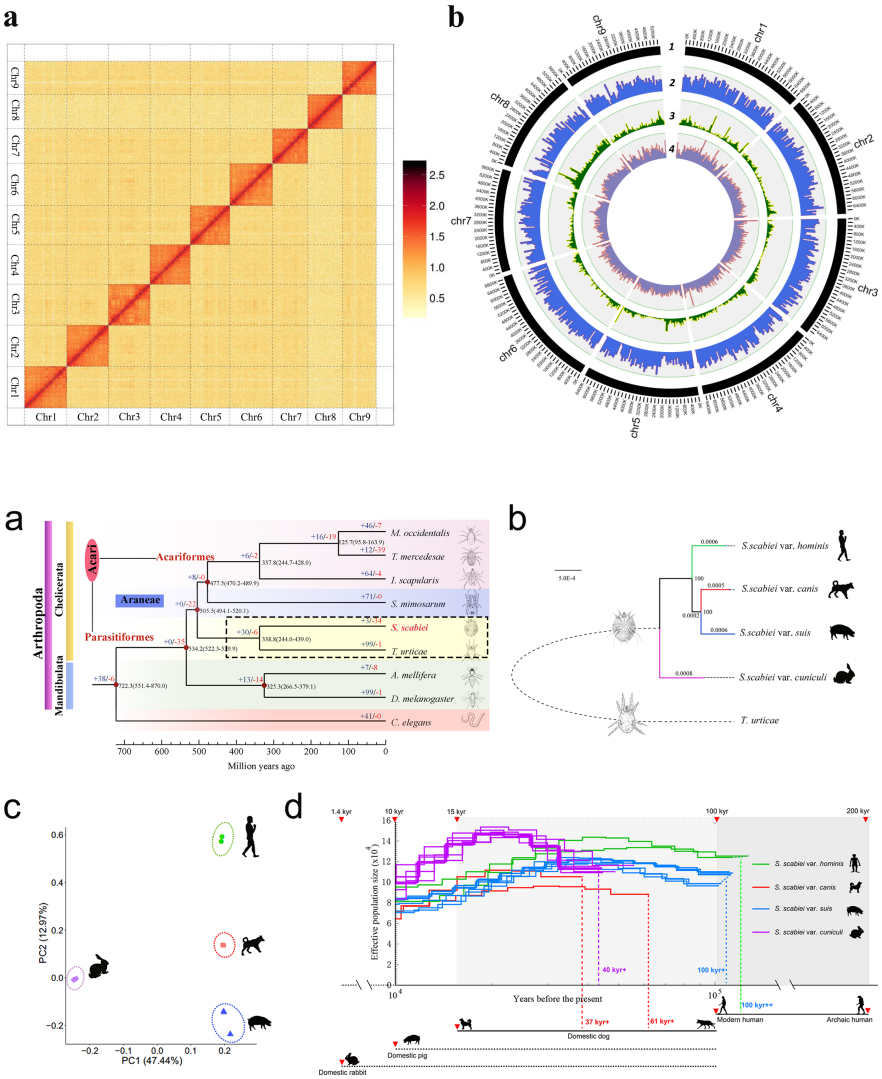
Figure 1. Heat map and genomic landscape of the*S. scabiei* var. *cuniculi* genome. (a) Heat map of the*S. scabiei* var. *cuniculi* genome. (b) Genomic landscape of the *S. scabiei* var. *cuniculi* assembly over 100-kb chromosomal intervals. Tracks from outside to inside: 1. Positions of the nine chromosomes of *S. scabiei* ; 2. Gene density; 3. Repeat sequences across the genome; 4. GC content.

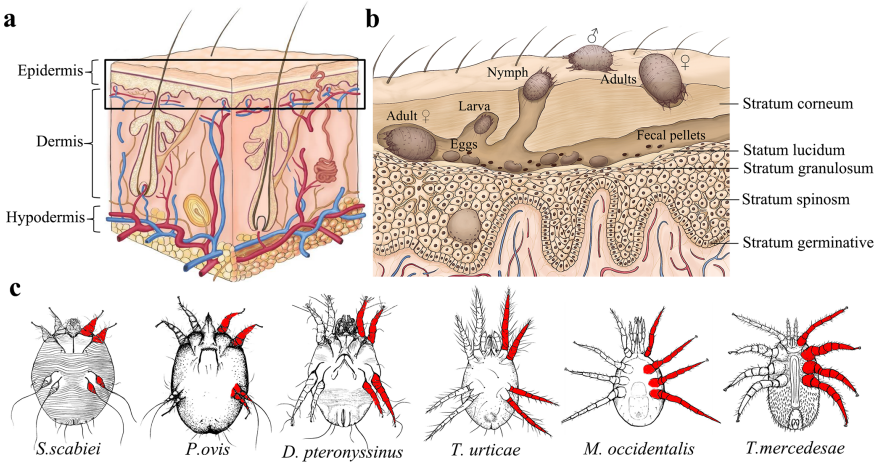
Figure 2. Evolution of the scabies mite genome. (a) Phylogenetic tree of *S. scabiei* var. *cuniculi* constructed using 1,338 shared single-copy orthologous genes and estimation of divergence time and expansion and contraction in gene families. (b) Genetic relationship of *S. scabiei* mite derived from four human, pig, dog and rabbit. (c) Principal component analysis (PCA) plot of*S. scabiei* populations using autosomal single nucleotide polymorphisms (SNPs). The fraction of the variance explained is 47.44% for eigenvector 1 and 12.97% for eigenvector 2. (d) Demographic history of *S. scabiei* variants**.** Ancestral population size was inferred using pairwise sequentially Markovian coalescence (PSMC). Data are shown individually for 20 mite populations. Generation time (g) = 0.0575 years, mutation rate (μ) = 5.8×10^{-9} mutations per bp per generation. Cartoon humans and animals in black represent the hosts of corresponding mite populations. Marked year on the top indicated the emerging of Archaic hunans and modern humans, as well as the domestication time of dogs, pigs and rabbits from currently available literatures.

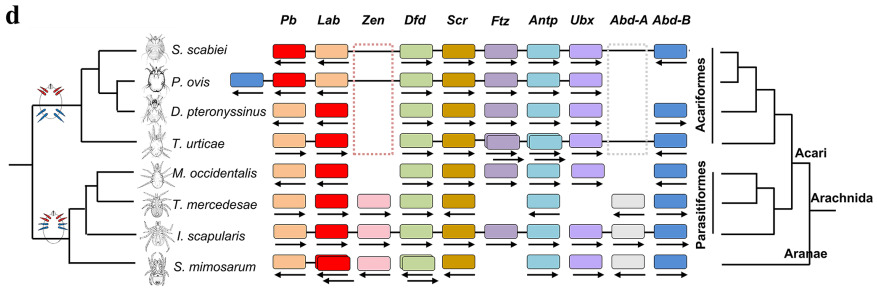
Figure 3. Morphology of representative mites in the Acari and organization of *Hox* genes . (a) Schematic diagram of mammal skin. (b) Life cycle of sarcoptic mites. (c) Morphology of six species of female mites. (d) Organization of *Hox* genes of *S. scabiei*and other chelicerate species. Left panel, phylogenetic relationship adapted from Figure 2a; central panel, *Hox* genes and transcript directions; right panel, traditional taxonomy.

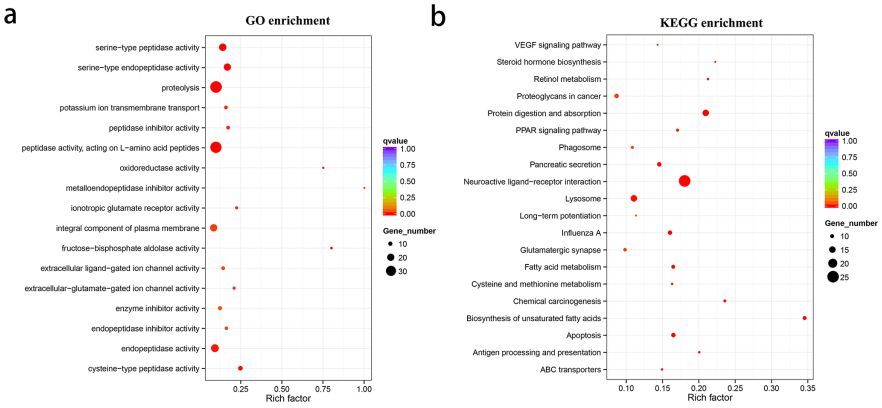
Figure 4. GO and KEGG enrichment of *S. scabiei* specific genes identified by orthoMCL. (a) GO. (b) KEGG.

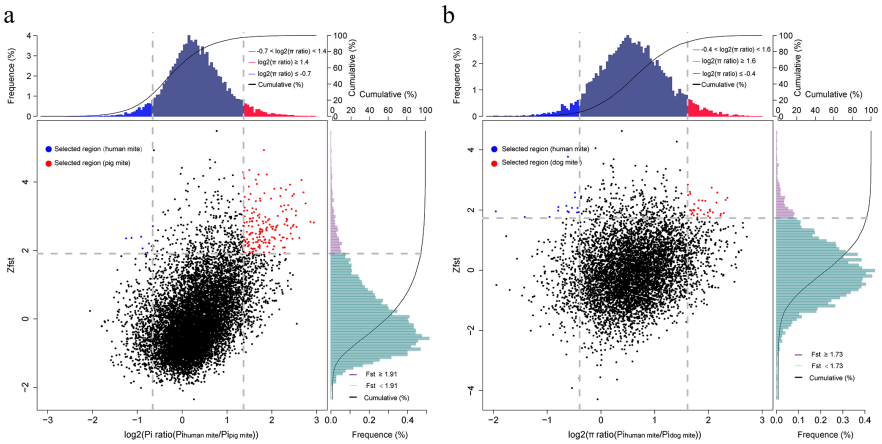
Φιγυρε 5. Διστριβυτιον οφ ϑπ ρατιος ανδ *ΦΣΤ* αλυες, ωηιςη αρε ςαλςυλατεδ ιν 10-κβ ωινδοως σλιδινγ ιν 5-κβ στεπς. (a) Genomic regions with strong selective sweep signals between human mites and pig mites. Data points located to the left and right of the left and right vertical dashed lines, respectively (corresponding to the 5% left and right tails of the empirical $\vartheta\pi$ ratio distribution, where the $\vartheta\pi$ ratios are -0.7 and 1.4, respectively), and above the horizontal dashed line (the 5% right tail of the empirical FST distribution, where FST is 1.91) were identified as selected regions for human mites (blue points) and pig mites (red points), respectively. (b) Genomic regions with strong selective sweep signals between human mites and dog mites. Data points located to the left and right of the left and right vertical dashed lines, respectively (corresponding to the 5% left and right tails of the empirical $\vartheta\pi$ ratio distribution, where the $\vartheta\pi$ ratios are -0.7 and 1.4, respectively), and above the horizontal dashed line (the 5% right tail of the empirical FST distribution, where FST is 1.91) were identified as selected regions for human mites (blue points) and dog mites (red points), respectively.











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