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Genomics of Host-Restricted Pathogens of the Genus *Bartonella*

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Abstract

The α-proteobacterial genus *Bartonella* comprises numerous arthropod-borne pathogens that share a common host-restricted life-style, which is characterized by long-lasting intraerythrocytic infections in their specific mammalian reservoirs and transmission by blood-sucking arthropods. Infection of an incidental host (e.g. humans by a zoonotic species) may cause disease in the absence of intraerythrocytic infection. The genome sequences of four *Bartonella* species are known, i.e. those of the human-specific pathogens *Bartonella bacilliformis* and *Bartonella quintana*, the feline-specific *Bartonella henselae* also causing incidental human infections, and the rat-specific species *Bartonella tribocorum*. The circular chromosomes of these bartonellae range in size from 1.44 Mb (encoding 1,283 genes) to 2.62 Mb (encoding 2,136 genes). They share a mostly synthenic core genome of 959 genes that features characteristics of a host-integrated metabolism. The diverse accessory genomes highlight dynamic genome evolution at the species level, ranging from significant genome expansion in *B. tribocorum* due to gene duplication and lateral acquisition of prophages and genomic islands (such as type IV secretion systems that adopted prominent roles in host adaptation and specificity) to massive secondary genome reduction in *B. quintana*. Moreover, analysis of natural populations of *B. henselae* revealed genomic rearrangements, deletions and amplifications, evidencing marked genome dynamics at the strain level.
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Until the early 1990s, the genus *Bartonella* comprised a single species, *B. bacilliformis*. Since then, the reclassification of previously described bacteria based on 16S rRNA sequences (i.e., *Grahamella* and *Rochalimea*) and the description of novel *Bartonella* species isolated from various animal reservoirs resulted in a major expansion of the genus to currently 19 approved species, one of which *(Bartonella vinsonii)* is split into 3 subspecies. Among those, nine have been associated with human diseases (fig. 1) [1, 2]. The arthropod-borne bartonellae are widespread pathogens that colonize mammalian endothelial cells and erythrocytes as major target cells [3]. While endothelial cells and potentially other nucleated cells may get infected in both reservoir and incidental hosts, erythrocyte invasion takes place exclusively in the reservoir host,

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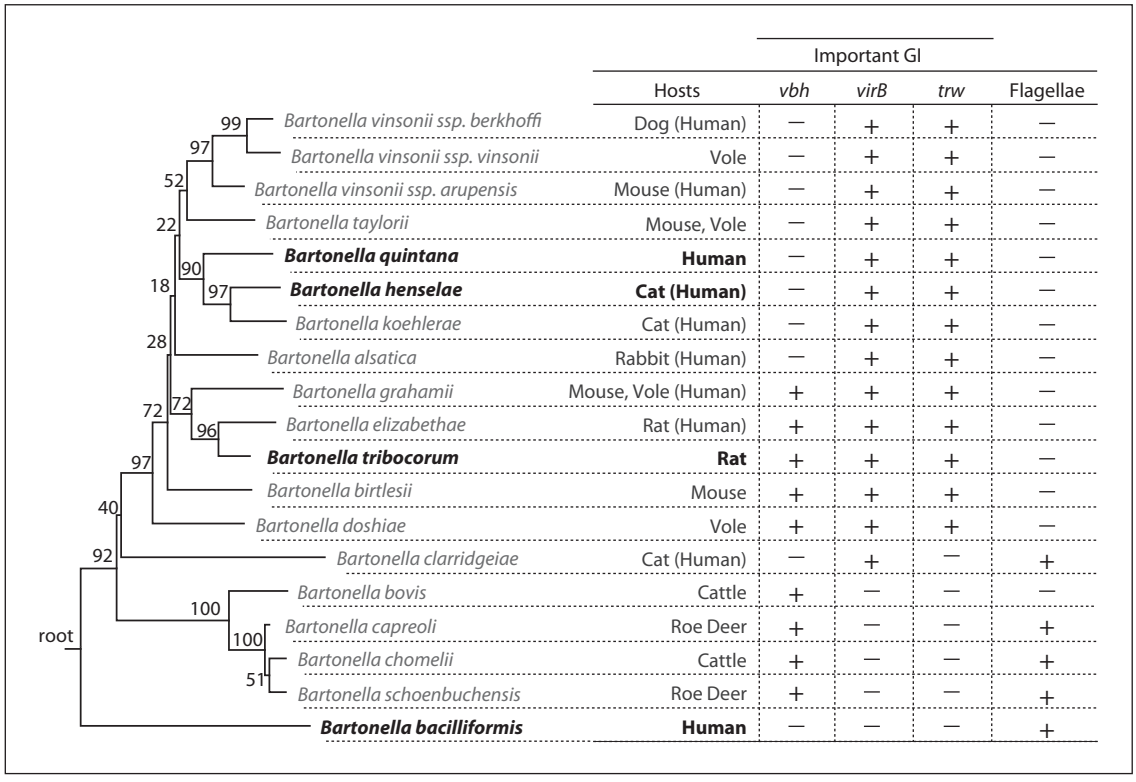

Fig. 1. Phylogeny and epidemiology of the genus *Bartonella*, distribution of important genomic islands (GI) encoding virulence factors, and presence/absence of flagella. For zoonotic species, man as an incidental host is indicated in brackets. Species with known genome sequences are highlighted in bold. The phylogenetic tree was calculated on the basis of protein sequences of *rpoB*, *groEL*, *ribC*, and *gltA* as described by [9]. Numbers at the nodes of the tree indicate bootstrap values for 1,000 replicates. Except for *Bartonella talpae* and *Bartonella peromysci,* for which no type strains exist, all approved species are included in the tree.

resulting in the establishment of a long-lasting intraerythrocytic bacteremia. Despite the fact that most *Bartonella* species are restricted to one reservoir host, there is an increasing body of evidence that some species can infect several different mammalian hosts [4–8]. The bartonellae represent an interesting model to study the evolution of host adaptation/host restriction as most mammals infested by blood-sucking arthropods serve as a reservoir host for at least one *Bartonella* species [9].

The highly virulent human-specific pathogen *B. bacilliformis* (causing life-threatening Oroya fever and verruga peruana) holds an isolated position in the *Bartonella* phylogeny as sole representative of an ancestral lineage. All other species evolved in a separate 'modern' lineage by radial speciation. These modern species represent host-adapted pathogens of rather limited virulence potential within their diverse mammalian reservoirs. Examples are the human-specific species *B. quintana* causing trench

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Table 1. General features of *Bartonella* genome sequences. PCG, protein-coding genes; n.d., not determined. The coding content of *B. bacilliformis* and *B. tribocorum* were (re-)calculated by dividing the total length of all protein-coding genes and tRNA/rRNA coding regions by the chromosome length. In addition, the average length of PCG was calculated for *B. bacilliformis* by dividing the total length of all PCG by the number of PCG.

	B. bacilliformis	*B. tribocorum*	*B. henselae*	*B. quintana*
Chromosome size	1,445,021 bp	2,619,061 bp	1,931,047 bp	1,581,384 bp
G+C content	38.2%	38.8% (35.0%)[a]	38.2%	38.8%
Total number of PCG	1,283	2,136 (18)[a]	1,488	1,142
Average length of PCG	909 bp	906 bp	942 bp	999 bp
Integrase remnants	n.d.	47 (0)[a]	43	4
Number of rRNA operons	2	2 (0)[a]	2	2
Number of tRNA genes	44	42 (0)[a]	44	44
Percentage coding	81.6%	74.6% (69.8%)[a]	72.3%	72.7%
Plasmid	0	1 (23,343 bp)[a]	0	0

[a] Numbers in brackets refer to the plasmid

fever, the cat-adapted zoonotic pathogen *B. henselae* causing cat-scratch-disease and various other disease manifestations in the incidental human host, and the rat-specific pathogen *B. tribocorum* not yet associated with human infection (fig. 1). Over the last decade, the availability of animal and cell culture infection models in combination with powerful bacterial genetics has facilitated research aiming at understanding the cellular and molecular interactions that contribute to the complex relationship between *Bartonella* and its mammalian hosts [1–3]. More recently, *Bartonella* has entered the post-genomic era by the release of several complete genome sequences. Here, we summarize the comparative and functional genomic studies on *Bartonella* that have been reported to date.

General Features of *Bartonella* Genomes

Complete genome sequences are presently available for four *Bartonella* species, i.e., *B. henselae* and *B. quintana* [10], *B. tribocorum* [9], and *B. bacilliformis* (GenBank accession no. CP000525). Additionally, the genome composition of *Bartonella koehlerae* has been analyzed by comparative genomic hybridization profiling (CGH) based on the genome sequence of the closely related species *B. henselae* [11]. The four available *Bartonella* genomes are composed of single circular chromosomes (plus one plasmid in *B. tribocorum*), which display a uniformly low G+C content of 38.2% to 38.8%, and a noteworthy low coding density of 72.3% to 81.6% (table 1). The chromosome sizes range from 1,445 kb (encoding 1,283 genes) for *B. bacilliformis* to 2,619 kb (encoding

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2,136 genes) for *B. tribocorum* (table 1, fig. 2). Orthologous gene assignments resulted in the identification of a core genome of 959 genes [9], which is encoded by a rather well conserved chromosomal backbone in a largely synthenic manner (fig. 2, see dotplots).

The relatively small core genome of the bartonellae reflects specific adaptations to the genus-specific lifestyle. For instance, a striking example of host-integrated metabolism is represented by hemin. This important source for iron and porphyrin is particularly abundant in the host niches colonized by bartonellae, i.e. the intracellular space of erythrocytes and the midgut lumen of blood-sucking arthropods. The strict hemin requirement for growth of *B. quintana* (and probably other bartonellae) in vitro correlates with the presence of multiple genes encoding hemin binding and hemin uptake proteins, while no hemin biosynthesis enzyme is encoded by this organism [10]. A large-scale mutagenesis screen in the *B. tribocorum*-rat model identified several of the hemin-uptake genes as essential for establishing intraerythrocytic infection. Moreover, this screen revealed that the majority of pathogenicity factors required for establishing intraerythrocytic bacteremia is encoded by the core genome inferred from the four available *Bartonella* genome sequences (66 of 97 pathogenicity genes) [9], indicating that this genus-specific infection strategy is to a large extent dependent on a conserved set of core genome-encoded pathogenicity factors.

Genome Dynamics by Lineage-Specific Expansion and Reduction

Despite of a largely synthenic core genome, the known *Bartonella* genomes are diversified by the variable size and composition of their accessory genomes. These were shaped in evolution by massive expansions (due to lateral gene transfer and gene duplication) and reductions (due to gene decay and deletion), which mostly occurred in a lineage-specific manner.

A marked example for genome reduction is *B. quintana*, which shares 1,106 orthologous genes with *B. henselae* as its closest relative (fig. 1). *B. henselae* codes for 382 genes without orthologs in *B. quintana*, while only 36 genes are unique to *B. quintana* [9, 10]. Interestingly, *Rickettsia prowazekii* representing another pathogen transmitted by the human body louse has also undergone recent genome reduction, suggesting that the extensive genome decay in the *B. quintana* lineage may be related to the biology of this arthropod vector [10]. However, *B. bacilliformis*, a pathogen vectored by the sandfly *Lutzomyia verrucarum*, displays also a remarkably small genome sequence, indicating that adaptation to humans could be accompanied by reductive genome evolution. Consistently, several of the more recently evolved human-specific pathogens display marked genome decay, e.g. *Salmonella typhi* and *Mycobacterium leprae* [12].

With an accessory genome exceeding the size of the core genome (1,195 vs. 959 genes), *B. tribocorum* represents a remarkable example of lineage-specific genome

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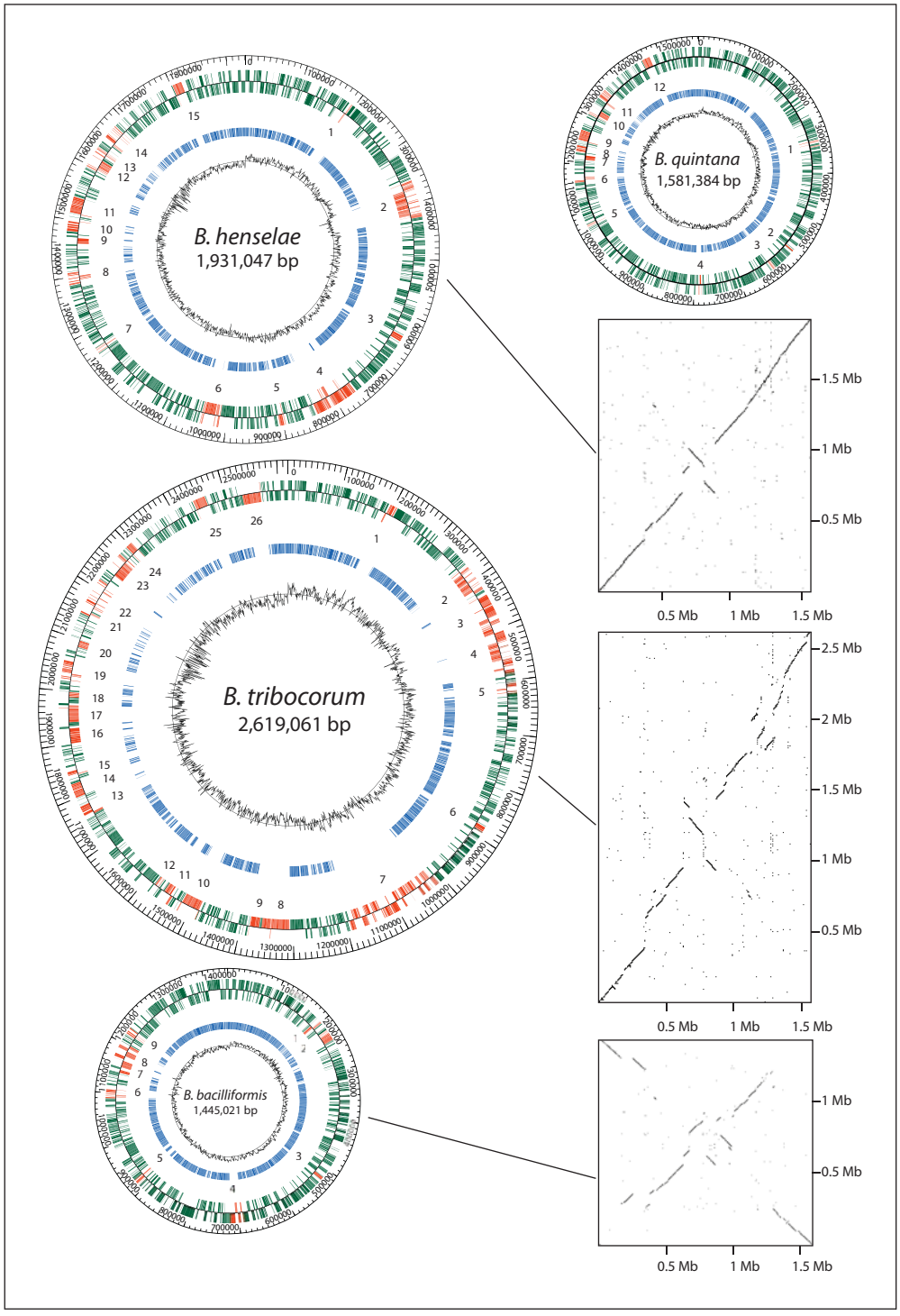

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expansion, and to a lesser extent genome expansion is also evident in *B. henselae* (accessory genome of 529 genes). The primary source for these genome expansions are prophages and other laterally acquired genomic islands (GIs, table 2 and fig. 2). One phage-related GI is conserved in all known *Bartonella* genomes (table 2; BB-GI2 and homologs). *B. tribocorum* and *B. henselae* encode in addition large (>50 kb) prophage regions (table 2; BH-GI2, BT-GI2/4) that are homologous but highly plastic in their genetic organization [10]. These mosaic prophage regions and the related GIs encoding homologous phage genes were probably shaped during evolution by a consecutive acquisition of different prophages, followed by duplication, excision, reintegration, and reduction of prophage segments of different size and origin. Exclusively *B. tribocorum* encodes another large prophage (>30 kb) that, moreover, is present in multiple copies (table 2; BT-GI8/10/17/26). The different copies of this prophage display a strictly conserved gene order (fig. 3a) and a marked similarity to the genetic organization and sequence of P2- and Mu-like prophages described in other bacterial taxa. GIs encoding two-partner secretion systems, which often also carry phage genes, have also contributed to the large accessory genomes of *B. tribocorum* and *B. henselae* (table 2; BH-GI4/6, and BT-GI3/7/9/11). Remnants of these GIs are found in the reduced genome of *B. quintana*, while they are absent from the ancestral *B. bacilliformis* lineage and closely related α-proteobacterial taxa. A prototype of these GIs was thus likely acquired by the common ancestor of the modern *Bartonella* lineage, followed by lineage-specific expansions and reductions. At present it is unknown whether the prophages, phage-related GIs and GIs encoding two-partner secretion systems, that contributed to the remarkable genome expansion exemplified by *B. tribocorum* and *B. henselae*, have any beneficial role in host interaction, or whether these two species are just not under the selective pressure that resulted in massive genome reduction in *B. quintana*.

Some other GIs constituting the accessory genomes of the bartonellae are well established pathogenicity factors with important roles in the process of host colonization. Unlike *B. bacilliformis*, all species of the modern lineage encode at least one of the closely related type IV secretion systems (T4SSs) VirB/VirD4 or Vbh (VirB homolog) (fig. 1), which likely emanated from an ancestral duplication event and which are redundant in function. These VirB-like T4SSs are considered to represent major host adaptability factors that contributed to the remarkable evolutionary success of the modern lineage [9]. T4SSs are transporters ancestrally related to bacterial conjugation systems that mediate the vectorial translocation of virulence factors across the

Fig. 2. Circular genome maps of the four *Bartonella* genome sequences and Dot-plot representation of genome colinearity (micro-syntheny). The genome maps indicate (outside circles to inside circles) the genes on the + and – strands (genes located on genomic islands which are >5 kb or encoding more than five CDS are colored in red, all other genes in green), the genes belonging to the core genome (in blue), and the GC skew (black). Dot-plots were plotted for the *B. quintana* genome against any other genome for a sliding window of 20 nucleotides. Numbers in the genome circles refer to the different genomic islands (see also table 2).

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Table 2. List of genomic islands (GIs) >10 kb of the four known *Bartonella* genomes. The first and last gene of each island is indicated by its locus tag (only the number of each locus tag is shown). The length refers to the start and end of the first and last gene of the island, respectively.

GI#	Similar genomic Islands	Description	tRNA	Begin	End	Length
B. bacilliformis						
BB-GI2	BT-GI20/23, BH-GI6/12, BQ-GI10	*Bartonella*-specific island encoding phage genes	yes	0217	0240	22115
BB-GI4		duplicated genomic region encoding housekeeping genes	no	0679	0710	26295
BB-GI5		conserved exported protein and transporter encoding genes	yes	0883	0894	10151
BB-GI6		conserved exported protein and phage genes	yes	1055	1080	17466
BB-GI8	BT-GI13, BH-GI10, BQ-GI8	flagella genes and inducible *Bartonella* autotransporter (*iba*) genes	yes	1116	1160	46499
BB-GI9		conserved exported protein and phage-related genes	no	1180	1190	12068
B. tribocorum						
BT-GI1		BT-specific helicase and phage-related genes	yes	0156	0167	15612
BT-GI2	BH-GI2, BQ-GI1	phage island	yes	0303	0377	51254
BT-GI3	BH-GI4/6	type II secretion system island	yes	0387	0422	44997
BT-GI4	BH-GI2/6	phage island	yes	0423	0564	110682
BT-GI5		BT-specific island encoding predicted membrane proteins	yes	0577	0596	17292
BT-GI6	BH-GI3, BQ-GI2, BB-GI3	putative membrane proteins not present in other alphaproteobacteria	no	0832	0834	11826
BT-GI7	BH-GI2/4/5/6	phage genes, type II secretion systems and helicase genes	yes	0941	1122	181527
BT-GI8		BT-specific phage island I	yes	1218	1283	53256
BT-GI9		BT-specific type II secretion systems and hypothetical genes	yes	1292	1301	18348
BT-GI10		BT-specific phage island II	yes	1382	1429	37682
BT-GI11	BH-GI4	type II secretion system island	no	1446	1464a	18888
BT-GI13	BH-GI10, BQ-GI8, BB-GI8	inducible *Bartonella* autotransporter (*iba*) genes	no	1650	1663	21879

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Table 2. Continued

GI#	Similar genomic Islands	Description	tRNA	Begin	End	Length
BT-GI14	BH-GI11, BQ-GI9	VirB T4SS and *Bartonella* effector protein (Bep) genes	no	1689	1710	25598
BT-GI16	BH-GI9, BQ-GI7, BB-GI7	conserved *Bartonella*-specific autotransporter encoding genes	no	1785	1796	28492
BT-GI17		BT-specific phage island III	yes	1810	1849	32182
BT-GI19	BH-GI8, BQ-GI6	transporter-associated genes, and restriction system specific to BT	yes	1897	1930	35415
BT-GI20	BH-GI6/12, BQ-GI10, BB-GI2	*Bartonella*-specific island encoding phage genes	yes	1965	1983	12384
BT-GI22	BH-GI14, BQ-GI11, BB-GI1	*Bartonella*-specific island encoding *yopP* gene(s) in BQ and BT	yes	2113	2225	53002
BT-GI23	BH-GI6/12, BQ-GI10, BB-GI2	*Bartonella*-specific island encoding phage genes	yes	2263	2306	37989
BT-GI24		VirB-homologous (Vbh) T4SS	no	2331	2351	13874
BT-GI25	BH-GI15, BQ-GI12	Trw T4SS	no	2507	2533	22519
BT-GI26		BT-specific phage island IV	yes	2603	2646	35567
B. henselae						
BH-GI2	BT-GI2/4/7, BQ-GI1	phage island	yes	02730	03760	65723
BH-GI4	BT-GI3/7/11	type II secretion system island	yes	06500	07260	75441
BH-GI6	BT-GI3/4/7/20/23, BQ-GI10, BB-GI2	phage genes and type II secretion	yes	08980	09500	33315
BH-GI8	BT-GI19, BQ-GI6	transporter-associated genes	yes	12470	12600	20850
BH-GI10	BT-GI13, BQ-GI8, BB-GI8	inducible *Bartonella* autotransporter (*iba*) genes	no	13120	13190	19100
BH-GI11	BT-GI14, BQ-GI9	VirB T4SS and *Bartonella* effector protein (Bep) genes	no	13250	13440	28575
BH-GI12	BT-GI20/23, BQ-GI10, BB-GI2	*Bartonella*-specific island encoding phage genes	yes	13900	14090	21639
BH-GI14	BT-GI22, BQ-11, BB-GI1	*Bartonella*-specific island	yes	14450	14630	29125
BH-GI15	BT-GI25, BQ-GI12	Trw T4SS	no	15530	15760	16156
B. quintana						
BQ-GI1	BT-GI2/4, BH-GI2	Remnants of phage island present in BH and BT	yes	02600	02760	12764
BQ-GI6	BT-GI19, BH-GI8	Transporter-associated genes	yes	09850	09930	10161
BQ-GI8	BT-GI13, BH-GI10, BB-GI8	inducible *Bartonella* autotransporter (*iba*) genes	no	10360	10410	12121

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Table 2. Continued

GI#	Similar genomic Islands	Description	tRNA	Begin	End	Length
BQ-GI9	BT-GI14, BH-GI11	VirB T4SS and *Bartonella* effector protein (Bep) genes	no	10510	10680	22110
BQ-GI10	BT-GI20/23, BH-GI6/12, BB-GI2	*Bartonella*-specific island encoding phage genes	yes	11020	11160	17399
BQ-GI11	BT-GI22, BH-GI14, BB-GI1	*Bartonella*-specific island encoding *yopP* gene(s) in BQ and BT	yes	11400	11630	20809
BQ-GI12	BT-GI25, BH-GI15	Trw T4SS	no	12450	12680	16587

two Gram-negative bacterial membranes and the host cell plasma membrane directly into the host cell cytoplasm [1]. The VirB/VirD4 T4SS of *B. henselae* was shown to translocate several effector proteins, termed Beps, into endothelial cells that subvert cellular functions, such as apoptosis and the inflammatory response, that are considered critical for establishing chronic infection [13–15]. The molecular mechanism by which VirB-like T4SSs mediate host adaptability is probably also dependent on the translocated Beps. Comparison of the *virB/virD4/bep* T4SS loci of *B. henselae*, *B. quintana* and *B. tribocorum* revealed that the *virB/virD4* genes encoding the 11 essential T4SS components are highly conserved, while the *bep* genes encoding the translocated Beps displayed a higher degree of sequence variation (fig. 3b), suggesting an increased rate of evolution as the result of positive selection for adaptive functions in the infected host [9].

A third T4SS, Trw, is present in a sub-branch of the modern lineage (fig. 1) and essential for the process of erythrocyte invasion [16]. Interestingly, the presence of Trw by the modern lineage correlates with the loss of flagella (fig. 1), which are required for the invasion of erythrocytes by *B. bacilliformis* and probably also the flagellated bacteria of the modern lineage [1]. Trw does not translocate any known effectors, but produces multiple variant pilus subunits due to tandem gene duplication and diversification (by combinatorial sequence shuffling and point mutations) of *trwL* (encoding the major pilus subunit TrwL) and *trwJ* (encoding the minor pilus-associated subunit TrwJ) (fig. 3c) [17]. The variant pilus subunits exposed on the bacterial surface are thought to facilitate the interaction with different erythrocyte receptors or blood group antigens, and may thus represent major determinants of host specificity [1].

Genome Dynamics on the Strain Level

Evidence for genome dynamics on the intra-species level is accumulating for different *Bartonella* species. To access the natural variation in gene content and genome

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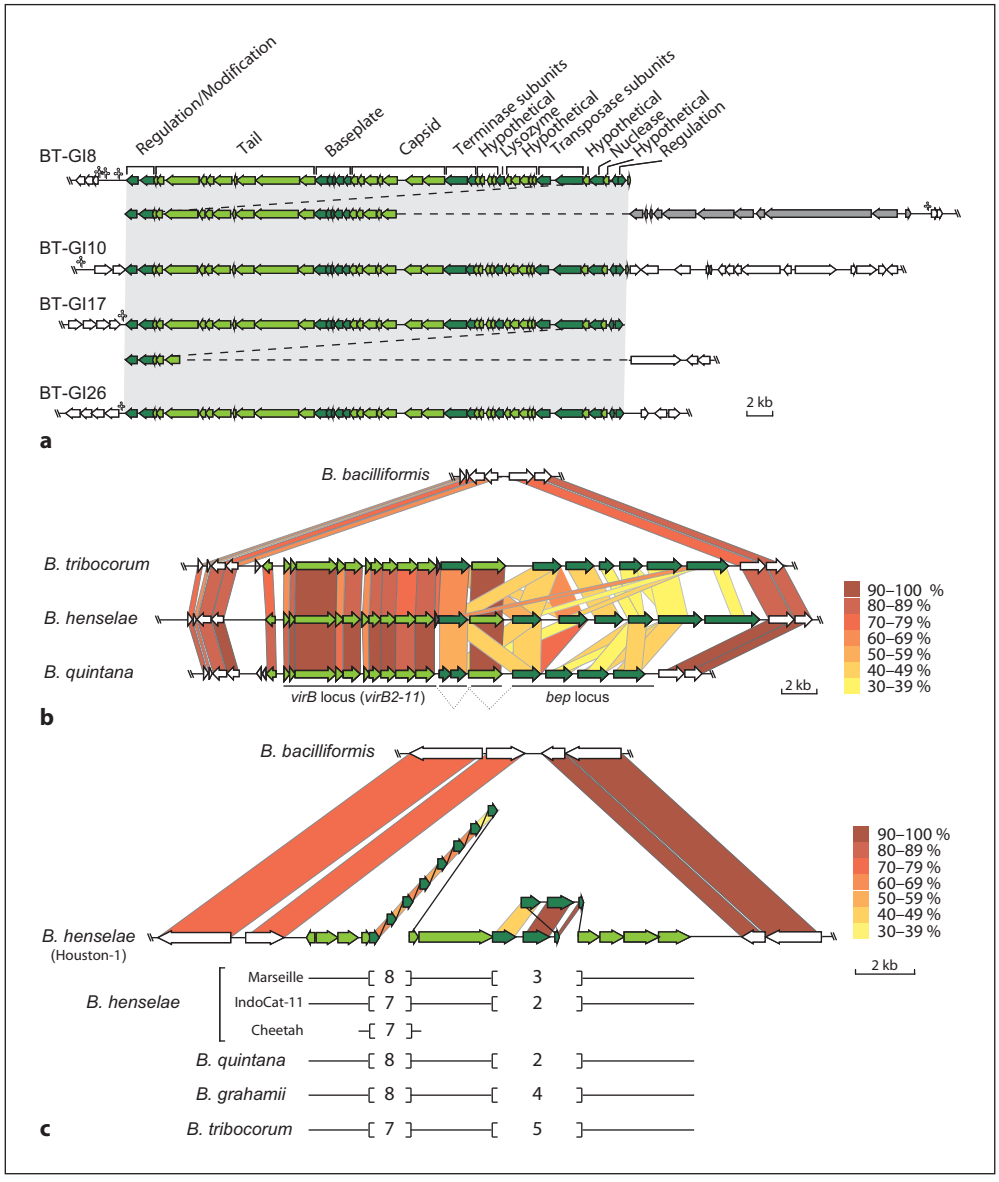

Fig. 3. Representation of selected GIs encoded in *Bartonella* genomes. Genes belonging to the GIs are shown in green, flanking genes are shown in white. (**a**) Alignment of the GIs encoding a *B. tribocorum*-specific prophage. Genes belonging to the prophage are located within the gray area. Noteworthy, BT-GI8 is flanked on one side by another island (gray gene symbols); (**b**) Alignment of the GI encoding the conserved T4SS VirB/VirD4 (*virB2–11* and *virD4* genes, colored in light green) and the highly variable translocated effectors (*bep* genes, colored in dark green); (**c**) Alignment of the GI (and flanking genes) encoding the T4SS-locus *trw*. The number of tandem repeats of *trwL* and *trwIJH* is indicated by gene symbols (colored in dark green) for the sequenced Houston-1 strain of *B. henselae* and by numbers in brackets for further *B. henselae* strains and the other species with known gene sequences. For (**b**) and (**c**), sequence similarity is shown with the percent identity indicated according to the color scales.

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structure of *B. henselae*, a set of 38 strains isolated from cats and humans was analyzed by comparative genome hybridization [18]. The variation in gene content was modest and confined to the mosaic prophage region and other GIs, whereas extensive rearrangements were detected across the terminus of replication with breakpoints frequently locating to GIs. Moreover, in some strains a growth-phase dependent DNA-amplification was detected that centered at a putative phage replication initiation site located in a large plasticity region exemplified by a particularly low coding density [18]. Another study suggested that *B. henselae* exists as a mosaic of different genetic variants in the infected host [19]. Finally, genomic rearrangements due to gene deletions were elegantly demonstrated in serial isolates of *B. quintana* from an experimentally infected macaque [20]. Together, these data strongly suggest that various mechanisms contribute to a dynamic genome variation on the strain level.

Conclusions

Comparative and functional analysis of the four available complete genome sequences of species belonging to the genus *Bartonella* yielded first insights into the evolution, ecology and host interaction of this largely understudied group of bacterial pathogens. The small core genome reflects a host-integrated metabolism and codes for the majority of genes involved in the genus-specific infection strategy characterized by long-lasting intraerythrocytic infections in specific mammalian reservoir hosts. However, it is also evident that the accessory genomes contribute significantly to this infection strategy, e.g. flagella serving in the process of erythrocyte invasion by more ancestral species are considered to be functionally replaced by a laterally-acquired T4SS in more recently evolved species. Other laterally-acquired T4SSs were associated with the remarkable host adaptability exemplified by the radiating modern lineage. Genome expansion by lateral gene transfer in combination with secondary genome reduction has shaped the variable accessory genomes of the known *Bartonella* genomes. Additional *Bartonella* genome sequences expected to get available in the near future should result in a better understanding of the evolutionary processes that facilitated the emergence of a radiating group of host-restricted pathogens adapted to colonize a large variety of mammalian species that is infested by blood-sucking arthropods.

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