Research Article

ATP-Binding Cassette Systems of Brucella

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Brucellosis is a prevalent zoonotic disease and is endemic in the Middle East, South America, and other areas of the world. In this study, complete inventories of putative functional ABC systems of five Brucella species have been compiled and compared. ABC systems of Brucella melitensis 16M, Brucella abortus 9-941, Brucella canis RM6/66, Brucella suis 1330, and Brucella ovis 63/290 were identified and aligned. High numbers of ABC systems, particularly nutrient importers, were found in all Brucella species. However, differences in the total numbers of ABC systems were identified (B. melitensis, 79; B. suis, 72; B. abortus 64; B. canis, 74; B. ovis, 59) as well as specific differences in the functional ABC systems of the Brucella species. Since B. ovis is not known to cause human brucellosis, functional ABC systems absent in the B. ovis genome may represent virulence factors in human brucellosis.

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1. Introduction

Brucella species are the causative agents of brucellosis, the world’s most prevalent zoonotic disease, with high occurrences in endemic areas including the Middle East, Asia, Mexico, and the Mediterranean [1]. The bacteria are small nonmotile, Gram-negative, nonspore-forming cocacobacilli that reside within the subphylum α-proteobacteria, which also includes nitrogen-fixing bacteria of the genus Nitrobacter, Rhizobium, Agrobacterium, and Rickettsia [2]. They are considered facultative intracellular pathogens.

There are six traditionally recognised Brucella species that have different host preferences: Brucella melitensis (which usually infects sheep and goats), Brucella abortus (cattle), Brucella suis (pigs), Brucella canis (dogs), and Brucella neotomae (desert wood rats). Furthermore, there are three newly identified Brucella species isolated from marine mammals: Brucella pinnipedialis (seals) [3], Brucella ceti (dolphins and porpoises) [3], and Brucella microti (voles) [4]. Although Brucella are primarily animal pathogens causing infectious abortions in females and orchitis in males [5], four of the nine species may infect humans (B. melitensis, B. abortus, B. suis, and occasionally B. canis, in order of disease severity) causing a range of flu-like symptoms including fever, sweats, malaise, and nausea [6]. Transmission to humans takes place via three recognised channels: (i) the consumption of infected animal products, (ii) direct contact with infected animal birth products, and (iii) the inhalation of aerosolised Brucella. Due to the nature of the human disease and the ability to be infectious via aerosol, Brucella species have been classified as category B threat agents by the US Centre for Disease Control and Prevention (CDC) [7].

Genome sequence analysis of B. melitensis 16M [8], B. suis 1330 [9], B. abortus 9-941 [10], B. canis RM6/66 (NCBI: NC_009504 and NC_009505, unpublished), and B. ovis 63/290 (NCBI: NC_010103 and NC_0010104, unpublished) has demonstrated the close relatedness of these organisms [11, 12]. The genomic DNA of each strain comprises two chromosomes of approximately 2.1 Mb and 1.2 Mb, DNA-DNA hybridisations between the species had previously revealed over 90% similarity between the species, leading to the suggestion that all Brucella species should be classified as B. melitensis [13, 14]. However, it is widely believed
that the differences in host specificity and pathogenicity are related to *Brucella* genetics; although there is currently little experimental evidence to support this, a few studies have found differences between the *Brucella* species genomes that may support this hypothesis [10, 15, 16]. A significant proportion of the *Brucella* genomes appear to code for ATP-binding cassette (ABC) systems.

ABC transporters are responsible for the import and export of many different substances across cellular membranes [17]. Although ABC transporters are extremely versatile, they all contain one defining feature, the ability to hydrolase ATP to ADP, providing the energy needed for active transport. ABCs have three main conserved motifs known as Walker A ([G-X-X-G-X-G-S/T], where X represents any amino acid residue), Walker B (ø-ø-ø-ø-D, where ø designates a hydrophobic residue), and a signature sequence ([LSGGQ]) [18]. The Walker A and Walker B motifs form tertiary structure enabling ATP-binding and can be found in all ATP-binding molecules. The signature sequence is well conserved in all ABC proteins and is also known as the linker peptide or C motif [19]. Although the configuration of ABC systems varies, the majority of ABC systems comprise of two hydrophilic ABC domains associated with two hydrophobic membrane-spanning domains (inner membrane (IM) proteins). Import systems are only found in prokaryotic organisms and contain both ABC domains and IM domains, along with extra- cytoplasmic binding proteins (BPs) designed to bind the specific allocrite of that ABC system. In Gram-negative bacteria the BPs are located in the periplasm whereas, in Gram-positive bacteria, they are anchored to the outer membrane of the cell via N-terminal lipid groups [20]. ABC systems import a diverse range of substrates into the bacterial cell including peptides [21], polyamines [22], metal ions [23], amino acids [24], iron [25], and sulphates [26]. In comparison, ABC systems involved in export functions usually contain only IM and ABC domains fused together via either the N-terminus (IM-ABC) or the C-terminus (ABC-IM), which homodimerise to create a functional system [27]. Substances exported by ABC transporters include antibiotics in both producing and resistant bacteria [28, 29], fatty acids in Gram-negative bacteria [27], and toxins [30]. In addition to transporters, many ABC proteins have roles in house-keeping functions, such as regulation of gene expression [31] and DNA repair [27, 32]. These proteins do not contain IM domains but are constituted of two fused ABC domains (ABC2) [27]. There is now increasing evidence that ABC systems can play roles in bacterial virulence [33–36] and can be used as targets for vaccine development [37].

The recent sequencing of the genomes of *B. melitensis* 16M [8], *B. abortus* 9-941 [10], *B. suis* 1330 [9], *B. ovis* 63/290 (NCBI: NC_009504 and NC_009505, unpublished), and *B. canis* RM6/66 (NCBI: NC_010103 and NC_0010104, unpublished) has enabled the genomic comparison of different *Brucella* species. We report the creation and comparison of reannotated inventories of the functional ABC systems in *Brucella*. This improved annotation has assisted in understanding *Brucella* lifestyles and the identification of ABC systems that may be involved in virulence.

2. Methods

The prediction of ABC systems in sequenced bacterial genomes is based on annotation- and similarity-based homology assessment of identified or predicted ABC proteins from heterologous bacterial systems. The Artemis viewer (available from http://www.sanger.ac.uk) was used to visualise the sequenced genomes of *B. melitensis* 16 M, *B. suis* 1330, *B. abortus* 9-941, *B. canis* RM6/66, and *B. ovis* 63/290 [8–10]. Using the annotated genomes, ABC proteins were searched for using an array of related words, specifically “ATP-binding cassettes,” “binding protein,” or “outer membrane protein.” For completeness all proteins that were labelled as hypothetical or conserved hypothetical proteins were also checked. Hits from this search were compiled and then genes upstream and downstream were also checked to ensure that all genes from one system were found. After the genome searches were completed, protein sequences were aligned using the basic local alignment search tool (BlastP) against other ABC proteins using the ABC systems: Information on Sequence Structure and Evolution (ABCISSE) database [27, 38]. The ABCISSE database comprises 24000 proteins from 9500 annotated systems over 795 different organisms. Proteins searched against ABCISSE that scored a threshold e-value of $10^{-4}$ were assigned to an ABC family and subfamily based on the hits from the ABCISSE database. Where searches on ABCISSE were unclear or hits for multiple families were produced, proteins were aligned using BlastP searches against the Genbank protein database. Use of this larger database increased the number of positive hits and functions that could be assigned. An ABC system was defined as a series of contiguous ORFs that shared the same family, subfamily, and substrate. A complete signal sequence ([LSGGQ]) was identified in the majority of the ABC proteins identified, and all of the other ABC proteins contained remnants of a complete signal sequence. Walker A and Walker B sequences were not sought during these searches.

The ABC system inventories compiled in this study include systems that contain genes with predicted frame shift mutations and premature stop codons. For example, the *B. melitensis* 16M gene BMEII0099 is a known pseudogene with multiple premature stop codons. However, this gene is part of an ABC system that is encoded by another four genes (BMEII0098, BMEII00101, BMEII102, and BMEII0103), all of which are predicted to be functional; the mutation in BMEII0099 might render the whole system nonfunctional or it is possible that the other four genes could create a partially functional system. Due to the inability to determine the functionality of ABC systems using bioinformatic techniques, the ABC systems where one or more components were predicted to be nonfunctional were excluded from the total ABC system numbers and functions of the ABC systems. Within the genomes of all *Brucella* species single components of ABC systems (mainly BP) not attached to individual systems were located. These were included in ABC system inventories and termed lone components but were not included in total functional ABC system counts.
3. Results and Discussion

The genome structures of Brucella species are very similar [10–12], and although it is widely believed that the differences in Brucella species virulence and host preferences are related to their genetic composition, there is little experimental evidence to support this belief. However, there are a few studies that have uncovered differences between the genomes [10, 15, 16]. In this study, we have compared the presence of putative functional ABC systems in the genomes of B. melitensis 16M (BM), B. suis 1330 (BS), B. abortus 9-941 (BS), B. canis RM6/66 (BC), and B. ovis 63/290 (BO). In the original annotations of these genomes, a uniform nomenclature was not used and functional assignment of the systems varied considerably. Here we describe a reannotation of the ABC systems of these bacterial strains, leading to new predicted functions of the systems and predictions about how the individual components combine to form functional systems. Complete inventories of the ABC systems of BM, BS, BA, BC, and BO are shown in Table 1.

The Brucella strains investigated in this study all have approximately 3.3 Mb genomes comprising two chromosomes of approximately 2.1 Mb and 1.2 Mb. The total number of predicted functional ABC systems encoded by the genomes of the Brucella strains is similar but does show some variability (BM = 79, BS = 72, BA = 64, BC = 74, BO = 59). Our evaluation of the Brucella genomes confirms that these species encode a relatively high proportion of ABC system genes when compared to other bacteria [39], with an average of 8.8% of their genomes dedicated to predicted functional ABC system genes (if lone components and mutated genes are included this figure increases to 9.3%). This may reflect their relatedness to environmental α-proteobacteria such as Nitrobacter and Agrobacterium which also encode high numbers of ABC systems [39] that may assist in their survival in diverse conditions.

This work reports the first full inventories of ABC systems within five genome-sequenced Brucella strains. There are a number of specific ABC systems/genes that have previously been identified in the published literature. For example, Paulsen et al. describe two ABC systems that are present in B. suis and absent in B. melitensis. The first of these is an ABC importer encoded by BR0952 (IM), BR0953 (IM), and BR0955 (BP) [9]. Although this particular system is listed in the inventory, the ABC protein component of the system was not located in the BS genome and so this system was deemed incomplete and unlikely to be functional. The system was almost completely missing from the BM genome which is consistent with the findings of Paulsen et al. [9]. The second reported system is encoded by BRA0630, BRA0631, BRA0632, BRA0633, BRA0634, and BRA0635. However, when these genes were assessed using ABCISSE, only two of the five genes were predicted to be ABC transporter binding proteins (BRA0631 and BRA0632) and no other ABC components were located. Thus we deem this system also likely to be nonfunctional. Other genes that have been identified in the literature are BRA1080 (a dipeptide ABC transporter protein identified in BS), BME1742 (a mitochondrial export ABC transporter identified in BM), and BRA0749-BRA0750 (involved in oligopeptide import) [10], all of which are present in our inventories.

4. ABC System Functions

In this study, we have classified the ABC systems of BM, BS, BA, BC, and BO into classes, families, and subfamilies according to the functional classification system described by Dassa and Bouige [27] (Table 2). The Brucella strains encode 8–12 class 1 systems, characterised by an ABC-IM domain fusion and comprising predicted export systems, and 5 class 2 systems, characterised by a duplicated fused ABC and with predicted functions in antibiotic resistance and house-keeping functions. However, we have found that most of the ABC systems of Brucella species belong to class 3 with roles predicted in import processes. The further classification of Brucella ABC systems into families and subfamilies shows that there are a high number of ABC systems of specific importer families, particularly the MOI (minerals and organic ions), MOS (monosaccharides), OPN (oligosaccharides and nickel), OSP (oligosaccharides and polyols), and OTCN (osmoprotectants taurine cyanate and nitrate) families, all of which primarily function to acquire nutrients.

The predicted functionality of the ABC systems within the Brucella genomes is dominated by ABC systems involved in the import of nutrients (Figure 1), and although this is not uncommon amongst bacteria, it is probable that Brucella species utilise ABC transporters to provide most of the nutrients they require [8, 39]. In support of the findings of Paulsen et al. [9], the 2.1 Mb chromosome encodes a large proportion of the ABC systems involved in molecular export and cellular process whereas the ABC systems located on the smaller chromosome are largely biased toward nutrient acquisition, leading to the idea that this second chromosome is important in the acquisition and processing of nutrients in Brucella.

Since the ABC systems were identified by homology searches, it is possible to assign each ABC importer with a predicted substrate that it imports, providing an overview of the ABC system-based import ability of the Brucella species. Table 3 shows the range of predicted substrates imported via ABC transporters within the Brucella genomes. Overall, our results show that there is little difference in the import ability between strains of the four species of Brucella that are pathogenic to humans (BM, BS, BA, and BC). However, BO lacks the ability to import 8 of the 26 listed nutrients via ABC systems. In fact, all of the 29 pseudogenes that are present within the BO ABC system inventory occur within nutrient importers. The nutrients that BO appears to be unable to import using ABC systems include polyamines (specifically spermidine and putrescine), nickel, thiamine, glycin betaine, erythritol, xylose, and molybdenum. It is possible that the defective uptake of one or more of these substrates by B. ovis may contribute to its likely lack of virulence in humans. For example, polyamines have recently been associated with bacterial virulence and pathogenicity in human pathogens [40] and polyamine transporters have therefore been targeted as novel vaccine candidate targets for human pathogens [41, 42].
| Number | Family | Subfamily | Substrate/Function | Type | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|--------|--------|-----------|-------------------|------|--------------|------------|--------|---------|---------|
| 1      | ART    | REG       | Involved in gene expression regulation | ABC2 | BMEI0288     | BruAb11738 | BR1753 | BOV_1692 | BCAN_A1791 |
| 2      | ART    | REG       | Involved in gene expression regulation | ABC2 | BMEI0553     | BruAb11451 | BR1456 | BOV_1411 | BCAN_A1491 |
| 3      | ART    | REG       | Involved in gene expression regulation | ABC2 | BMEI1258     | BruAb10711 | BR0692 | BOV_0683 | BCAN_A0704 |
| 4      | CBY    | CBU       | Cobalt import     | ABC  | BMEI0635     | BruAb11365 | BR1368 | BOV_1324 | BCAN_A1395 |
| 5      | CCM    |           | Possibly heme export | IM   | BMEI1185     | BruAb11185 | BR0096 | ccmC     | BOV_0094 | BCAN_A0908, ccmC |
| 6      | CDI    |           | Involved in cell division | IM   | BMEI0273, ftsX | BruAb11971 | BR1996 | BCAN_A2042 |
| 7      | CLS    |           | O antigen export system | ABC  | BMEI1415, rfbD | BruAb11972, rfbD | BOV_1324 | rfbE     | BCAN_A0532, rfbD |
| 8      | DLM    | (ABCY)    | D-L-Methionine and derivatives import | LPP  | BMEI1954     |             |        |          |         |
| 9      | DLM    | (ABCY)    | D-L-Methionine and derivatives import | IM   | BMEI0336     | BruAb2071   | BRA0962 | BOV_A0903 | BCAN_B0983 |
| 10     | DPL    | CYD       | Cytochrome bd biogenesis and cysteine export | IM-ABC | BMEI0761, cydC | BruAb20713 | BRA0509 | cydD     | BOV_A0443 | BCAN_B0508 |
| 11     | DPL    | MDL       | Involved in mitochondrial export systems | IM-ABC | BMEI0323, msaA | BruAb11700 | BR1715 | BOV_A1657 | BCAN_A1753 |
| 12     | DPL    | HMT       | Involved in mitochondrial export systems | IM-ABC | BMEI0472     | BruAb11533  | BR1545 | BOV_A1493 | BCAN_A1581 |
| 13     | DPL    | PRT       | Proteases, lipase, S-layer protein export | OMP  | BMEI1029, ToIC | BruAb10954 | BR0998 | BCAN_A0957 |
| 14     | DPL    | CHV       | Beta-(1–>2) glucan export | IM-ABC | BMEI0984     | BruAb11004  | BR0998 | BCAN_A1015 |
| 15     | DPL    | HMT       | Heavy metal tolerance protein | IM-ABC | BMEI1152     | BruAb10321  | BR0442 | BOV_A0449 | BCAN_A0446 |
| 16     | DPL    | HMT       | Involved in mitochondrial export systems | IM-ABC | BMEI1743     |             |        |          |         |
| 17     | DPL    | LIP       | Involved in lipid A or polysaccharide export | IM-ABC | BMEI0250     | BruAb20990  | BRA0150 | BOV_A0988 | BCAN_B1071 |
| 18     | DRI    | YHHH      | Unknown            | IM   | BMEI0656     | BruAb11347  | BR1349 | BOV_1307 | BCAN_A1377 |
| 19     | DRI    | YHHH      | Unknown            | IM   | BMEI0655     |             |        |          |         |
| 20     | DRI    | NOS       | Nitrous oxide reduction | IM   | BMEI0970, nosY | BruAb20902, nosY | BRA0278, nosY | BOV_A0254 | BCAN_B0280 |
| 21     | FAE    |           | Fatty acid export  | IM-ABC | BMEI0520     | BruAb11484  | BR1490 | BOV_A0247 | BCAN_B0273 |
| 22     | FAE    |           | Fatty acid export  | IM-ABC | BMEI0976     | BruAb20908  |        |          |         |
| Number | Family | Subfamily | Type | Substrate/Function | E. coli | E. albertus | E. canis | E. abortus | E. ovis | E. suis | E. canis | B. melitensis |
|-------|--------|-----------|------|------------------|--------|------------|----------|------------|----------|--------|----------|------------|-------------|
| 23    | HAA    |          | IM   | Branched-chain amino acids | IMAI790 | BCAI1729 | BCAI1730 | BCAI1731 | BCAI1732 | BCAI1733 |
| 24    | HAA    |          | IM   | Branched-chain amino acids | IMAI791 | BCAI1734 | BCAI1735 | BCAI1736 | BCAI1737 | BCAI1738 |
| 25    | HAA    |          | IM   | Branched-chain amino acids | IMAI792 | BCAI1739 | BCAI1740 | BCAI1741 | BCAI1742 | BCAI1743 |
| 26    | HAA    |          | IM   | Branched-chain amino acids | IMAI793 | BCAI1744 | BCAI1745 | BCAI1746 | BCAI1747 | BCAI1748 |
| 27    | HAA    |          | IM   | Branched-chain amino acids | IMAI794 | BCAI1749 | BCAI1750 | BCAI1751 | BCAI1752 | BCAI1753 |
| 28    | HAA    |          | IM   | Branched-chain amino acids | IMAI795 | BCAI1754 | BCAI1755 | BCAI1756 | BCAI1757 | BCAI1758 |
| 29    | HAA    |          | IM   | Branched-chain amino acids | IMAI796 | BCAI1759 | BCAI1760 | BCAI1761 | BCAI1762 | BCAI1763 |
| 30    | HAA    |          | IM   | Branched-chain amino acids | IMAI797 | BCAI1764 | BCAI1765 | BCAI1766 | BCAI1767 | BCAI1768 |
| 31    | HAA    |          | IM   | Branched-chain amino acids | IMAI798 | BCAI1769 | BCAI1770 | BCAI1771 | BCAI1772 | BCAI1773 |

*Table 1: Continued.*
| Number | Family | Subfamily | Substrate/Function | Type  | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|--------|--------|-----------|-------------------|-------|---------------|-----------|--------|--------|---------|
| 32     | ISVH   | Iron siderophores, VB12 and Hemin import | ABC    | BMEI0660 | BruAb11342   | BR1344    | BOV1302 | BCAN_A1371 |
|        | ISVH   | Iron siderophores, VB12 and Hemin import | IM     | BMEI0659 | BruAb11343   | BR1345    | BOV1304 | BCAN_A1372 |
|        | ISVH   | Iron siderophores, VB12 and Hemin import | OM     | BMEI0657 | BruAb11344   | BR1347    | BOV1306 | BCAN_A1374 |
|        | ISVH   | Iron siderophores, VB12 and Hemin import | BP     | BMEI0658 | BruAb11345   | BR1346    | BOV1305 | BCAN_A1373 |
| 33     | ISVH   | Iron(III) dicitrate import | BP     | BMEI0355 | BruAb20476   | BRA0756   | BOV_A0705 | BCAN_B0763 |
|        | ISVH   | Iron(III) dicitrate import | IM     | BMEI0356, fecD | BruAb20477 | BRA0755   | BOV_A0704 | BCAN_B0764 |
|        | ISVH   | Iron(III) dicitrate import | ABC    | BMEI0357, fecE | BruAb20478 | BRA0754   | BOV_A0703 | BCAN_B0762 |
| 34     | ISVH   | Iron(III) import | ABC    | BMEI0604 | BruAb20550   | BRA0678   | BOV_A0635 | BCAN_B0677 |
|        | ISVH   | Iron(III) import | IM     | BMEI0605, fatC | BruAb20551 | BRA0676   | BOV_A0634 | BCAN_B0675 |
|        | ISVH   | Iron(III) import | IM     | BMEI0606, fatD | BruAb20552 | BRA0677   | BOV_A0633 | BCAN_B0676 |
|        | ISVH   | Iron(III) import | BP     | BMEI0607 | BruAb20553   | BRA0675   | BOV_A0632 | BCAN_B0674 |
| 35     | MET    | Zinc import | IM     | BMEI0176, ZnuB | BruAb21061, ZnuB | BRA1124, ZnuB | BOV_A1029 | BCAN_B1152 |
|        | MET    | Zinc import | ABC    | BMEI0177, ZnuC | BruAb21060, ZnuC | BRA1123, ZnuC | BOV_A1028 | BCAN_B1151 |
|        | MET    | Zinc import | BP     | BMEI0178, ZnuA | BruAb21059, ZnuA | BRA1122, ZnuA | BOV_A1027 | BCAN_B1150 |
| 36     | MKL    | Involved in toluene tolerance | ABC    | BMEI0964 | BruAb11025   | BR1020   | BOV_0987 |
|        | MKL    | Involved in toluene tolerance | IM     | BMEI0965, tgt2B | BruAb11024 | BR1019   | BOV_0986 |
|        | MKL    | Involved in toluene tolerance | SS     | BMEI0966, tgt2C | BruAb11026 | BR1021   | BOV_0988 |
| 37     | MOI    | Thiamine import | ABC    | BMEI0283, thiQ | BruAb11744 | BR1759   | BOV_1698 | BCAN_A1798 |
|        | MOI    | Thiamine import | IM     | BMEI0284, thiP | BruAb11743, thiP | BR1758, thiP | BOV_1696 | BCAN_A1797 |
|        | MOI    | Thiamine import | BP     | BMEI0285 | BruAb11744, thiB | BR1757, thiB | BOV_1695 | thIP, BCAN_A1796 |
| 38     | MOI    | Putrescine import | IM     | BMEI0411, potF | BruAb11599 | BR1612 | BOV_1556 | BCAN_A1649 |
|        | MOI    | Putrescine import | ABC    | BMEI0412 | BruAb11598 | BR1611 | BOV_1555 | BCAN_A1648 |
|        | MOI    | Putrescine import | IM     | BMEI0413 | BruAb11596 | BR1609 | BOV_1554 | BCAN_A1647 |
|        | MOI    | Putrescine import | BP     | BMEI0414 | BruAb11597 | BR1610 | BOV_1553 | BCAN_A1646 |
| 39     | MOI    | Sulphate import | IM     | BMEI0675, cysW | BruAb11328, cysW2 | BR1328, cysW2 | BOV_1288 | CysW, BCAN_A1353 |
|        | MOI    | Sulphate import | IM     | BMEI0674, cysT | BruAb11329 | BR1329 | BOV_1289 | CysT, BCAN_A1354 |
|        | MOI    | Sulphate import | BP     | BMEI0673 | BruAb11330 | BR1330 | BOV_1290 | CysA, BCAN_A0113 |
| 40     | MOI    | Sulphate import | IM     | BMEI1839, cysW | BruAb11016 | BR0110 | BOV_0107 | CysA, BCAN_A0112 |
|        | MOI    | Sulphate import | IM     | BMEI1840, cyst | BruAb11010, cysT | BR0108 | BOV_0105 | CysT, BCAN_A0111 |
|        | MOI    | Sulphate import | BP     | BMEI1841 | BruAb11014 | BR0107 | BOV_0104 | BCAN_A0110 |
| 41     | MOI    | Phosphate import | IM     | BMEI1986, pstB | BruAb12116, pstB | BR2141, pstB | BOV_2056 | BCAN_A2185, pstB |
|        | MOI    | Phosphate import | IM     | BMEI1987, pstA | BruAb12114, pstC | BR2139, pstC | BOV_2055 | BCAN_A2184, pstA |
|        | MOI    | Phosphate import | IM     | BMEI1988, pstC | BruAb12115, pstA | BR2140 | BOV_2054 | BCAN_A2183, pstC |
|        | MOI    | Phosphate import | BP     | BMEI1989 | BruAb12113 | BR2138 | BOV_2053 | BCAN_A2128 |
| 42     | MOI    | Molybdenum import | ABC    | BMEI0003, modC | BruAb20900 | BRA0090, modC | BOV_A0084 | BCAN_B0093, ModC |
|        | MOI    | Molybdenum import | IM     | BMEI0004, modB | BruAb20898 | BRA0089, modB | BOV_A0083 | BCAN_B0092, ModB |
|        | MOI    | Molybdenum import | BP     | BMEI0005 | BruAb20888 | BRA0088, modA | BOV_A0082 | BCAN_B0091 |
| 43     | MOI    | Spermidine/putrescine import | ABC    | BMEI0193, potA | BruAb21046 | BRA1107 | BCAN_B1129 |
|        | MOI    | Spermidine/putrescine import | IM     | BMEI0194, potB | BruAb21044 | BRA1106 | BCAN_B1128 |
|        | MOI    | Spermidine/putrescine import | IM     | BMEI0195, potC | BruAb21045 | BRA1105 | BCAN_B1127 |
|        | MOI    | Spermidine/putrescine import | BP     | BMEI0196 | BruAb21043 | BRA1104 | BCAN_B1126 |
| Number | Family | Subfamily | Strain | Type | Substrate/Function | Type | Strain | Type | Strain | Type | Strain | Type | Strain | Type |
|--------|--------|-----------|--------|------|-------------------|------|--------|------|--------|------|--------|------|--------|------|
| 44     | B. melitensis | | | | | | | | | | | | | |
| 45     | B. abortus | | | | | | | | | | | | | |
| 46     | B. suis | | | | | | | | | | | | | |
| 47     | B. ovis | | | | | | | | | | | | | |
| 48     | B. canis | | | | | | | | | | | | | |
| 49     | Unknown | | | | | | | | | | | | | |
| 50     | Unknown | | | | | | | | | | | | | |
| 51     | Unknown | | | | | | | | | | | | | |
| 52     | Unknown | | | | | | | | | | | | | |
| 53     | Unknown | | | | | | | | | | | | | |
| 54     | Unknown | | | | | | | | | | | | | |

Table 1: Continued.

| Number | Family | Subfamily | Strain | Type | Substrate/Function | Type | Strain | Type | Strain | Type | Strain | Type | Strain | Type |
|--------|--------|-----------|--------|------|-------------------|------|--------|------|--------|------|--------|------|--------|------|
| 55     | B. melitensis | | | | | | | | | | | | | |
| 56     | B. abortus | | | | | | | | | | | | | |
| 57     | B. suis | | | | | | | | | | | | | |
| 58     | B. ovis | | | | | | | | | | | | | |
| 59     | B. canis | | | | | | | | | | | | | |
| 60     | Unknown | | | | | | | | | | | | | |
| 61     | Unknown | | | | | | | | | | | | | |

Comparative and Functional Genomics
| Number | Family | Subfamily | Substrate/Function       | Type      | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|--------|--------|-----------|--------------------------|-----------|--------------|-----------|--------|--------|---------|
| 55     | MOS    |           | Ribose import            | ABC2      | BMEI0300,   | BruAb20239, | BRA0995,| BOV.0937| BCAN.104 |
|        | MOS    |           | Ribose import            | IM        | BMEI0301,   | BruAb20240, | BRA0993,| BOV.1053| BCAN.1051|
|        | MOS    |           | Ribose import            | IM        | BMEI0302,   | BruAb20239, | BRA0994,| BOV.0935| BCAN.1012|
|        | MOS    |           | Ribose import            | BP        | BruAb20238  | BMEI0300,   | BRA0996,| BOV.0938| BCAN.1015|
| 56     | MOS    |           | Monosaccharide import    | BP        | BMEI0360,   | BruAb20296  | BRA0937| BOV.0879| BCAN.0957|
|        | MOS    |           | Monosaccharide import    | IM        | BMEI0361    | BruAb20297  | BRA0936| BOV.0878| BCAN.0956|
|        | MOS    |           | Monosaccharide import    | IM        | BMEI0362    | BruAb20298  | BRA0935| BOV.0877| BCAN.0955|
| 57     | MOS    |           | Erythritol import        | ABC2      | BMEI0432,   | BruAb20371, | BRA0860,| BOV.0807,| BCAN.0877|
|        | MOS    |           | Erythritol import        | IM        | BMEI0433,   | BruAb20372, | BRA0859,| BOV.0876| BCAN.0867|
|        | MOS    |           | Erythritol import        | BP        | BMEI0435    | BruAb20373, | BRA0858,| BOV.0805| BCAN.0875|
| 58     | MOS    |           | Galactoside/Ribose import| ABC2      | BMEI0698    | BruAb20654  | BRA0570| BOV.0533| BCAN.0570|
|        | MOS    |           | Galactoside/Ribose import| IM        | BMEI0700    | BruAb20655  | BRA0568| BOV.0534| BCAN.0567|
|        | MOS    |           | Galactoside/Ribose import| IM        | BMEI0701    | BruAb20656  | BRA0569| BOV.0535| BCAN.0568|
|        | MOS    |           | Galactoside/Ribose import| BP        | BMEI0702    | BMEI0361    | BRA0567| BOV.0532| BCAN.0567|
| 59     | MOS    |           | Monosaccharide import    | IM        | BMEI0981    | BruAb20913  | BRA0267| BOV.0242| BCAN.0268|
|        | MOS    |           | Monosaccharide import    | ABC2      | BMEI0982    | BruAb20914  | BRA0266| BOV.0241| BCAN.0267|
|        | MOS    |           | Monosaccharide import    | BP        | BMEI0983    | BruAb20916  | BRA0265| BOV.0240| BCAN.0266|
| 60     | o228   |           | Unknown                   | IM        | BMEI0361    | BruAb10085  | BRA0087| BOV.0085| BCAN.1712|
|        | o228   |           | Unknown                   | MFP       | BMEI0359    | BruAb10084  | BRA0086| BOV.0084| BCAN.1711|
|        | o228   |           | Unknown                   | ABC       | BMEI0360    | BruAb10084  | BRA0086| BOV.0084| BCAN.1711|
| 61     | o228   |           | Unknown                   | IM        | BMEI1138,   | BruA11658   | BR1671 | BOV.1617| BCAN.0839|
|        | o228   |           | Unknown                   | IM-ABC    | BMEI1139,   | BruA11657   | BR1670 | BOV.1616| BCAN.0839|
|        | o228   |           | Lipoprotein release system| ABC       | BMEI1138,   | BruA10838,  | BR0824,| BOV.0818| BCAN.0839|
|        | o228   |           | Lipoprotein release system| IM        | BMEI1139,   | BruA10838,  | BR0823,| BOV.0817| BCAN.0838|
| 64     | OPN    |           | Dipeptide import          | ABC       | BMEI0438,   | BruA11569   | BR1582 | BOV.1527| BCAN.1617|
|        | OPN    |           | Dipeptide import          | ABC       | BMEI0437,   | BruA11570   | BR1583 | BOV.1528| BCAN.1618|
|        | OPN    |           | Dipeptide import          | IM        | BMEI0435,   | BruA11571   | BR1584 | BOV.1530| BCAN.1620|
|        | OPN    |           | Dipeptide import          | IM        | BMEI0436,   | BruA11572   | BR1585 | BOV.1529| BCAN.1619|
|        | OPN    |           | Dipeptide import          | BP        | BMEI0433,   | BruA11573   | BR1586 | BCAN.1621|
| 65     | OPN    |           | Oligopeptide import       | ABC2      | BMEI1938,   | BruA10006   | BR0006 | BOV.0006| BCAN.0006|
|        | OPN    |           | Oligopeptide import       | BP        | BMEI1934    | BruA10007   | BR0007 | BOV.0009| BCAN.0010|
|        | OPN    |           | Oligopeptide import       | BP        | BMEI1935    | BruA10008   | BR0008 | BOV.0010| BCAN.0009|
|        | OPN    |           | Oligopeptide import       | IM        | BMEI1936,   | BruA10009   | BR0009 | BOV.0008| BCAN.0008|
|        | OPN    |           | Oligopeptide import       | IM        | BMEI1937,   | BruA10010   | BR0010 | BOV.0007| BCAN.0007|
| Number | Family | Subfamily | Substrate/Function | Type | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|--------|--------|-----------|-------------------|------|---------------|------------|--------|---------|---------|
| 66     | OPN    |           | Oligopeptide import | ABC  | BMEII0199, oppE | BruAb21039 | BRA100 |         | BCAN_B1123 |
| OPN    |        |           |                   | ABC  | BMEII0200, oppD | BruAb21040 | BRA101 |         | BCAN_B1122 |
| OPN    |        |           |                   | IM   | BMEII0201, oppC | BruAb21037 | BRA099 |         | BCAN_B1121 |
| OPN    |        |           |                   | IM   | BMEII0202, oppB | BruAb21038 | BRA098 |         | BCAN_B1119 |
| OPN    |        |           |                   | BP   | BMEII01203     | BruAb21036 | BRA097 |         |           |
| 67     | OPN    |           | Dipeptide import  | ABC  | BMEII0205, dppF | BruAb21033 | BRA1095| BOV_A0950| BCAN_B1117 |
| OPN    |        |           |                   | ABC  | BMEII0206, dppD | BruAb21034 | BRA1094| BOV_A0951| BCAN_B1116 |
| OPN    |        |           |                   | IM   | BMEII0207, dppC | BruAb21031 | BRA1093|         | BCAN_B1115, dppC |
| OPN    |        |           |                   | IM   | BMEII0209, dppB | BruAb21032 | BRA1092| BOV_A0952|           |
| OPN    |        |           |                   | IM   | BMEII0210      | BruAb21030 | BRA1090| BOV_A0954| BCAN_B1113 |
| 68     | OPN    |           | Dipeptide/ Oligopeptide import | BP   | BMEII0217      | BruAb21024 | BRA1084|         | BCAN_B107 |
| OPN    |        |           |                   | IM   | BMEII0220      | BruAb21020 | BRA1081|         | BCAN_B104 |
| OPN    |        |           |                   | IM   | BMEII0221      | BruAb21021 | BRA1080|         | BCAN_B103 |
| OPN    |        |           |                   | ABC  | BMEII0222      | BruAb21018 | BRA1079|         | BCAN_B102 |
| OPN    |        |           |                   | ABC  | BMEII0223      | BruAb21019 | BRA1078|         | BCAN_B101 |
| 69     | OPN    |           | Dipeptide import  | BP   | BMEII0284      | BruAb20952 | BRA1012| BOV_A0504| BCAN_B1032 |
| OPN    |        |           |                   | IM   | BMEII0285      | BruAb20950 | BRA1009| BOV_A0501| BCAN_B1031 |
| OPN    |        |           |                   | IM   | BMEII0286      | BruAb20951 | BRA1008| BOV_A0502| BCAN_B1030 |
| OPN    |        |           |                   | ABC  | BMEII0287      | BruAb20948 | BRA1011| BOV_A0500| BCAN_B1029 |
| OPN    |        |           |                   | ABC  | BMEII0288      | BruAb20949 | BRA1010| BOV_A0501| BCAN_B1028 |
| 70     | OPN    |           | Nickel import     | BP   | BMEII0487      | BruAb20428 | BRA0804| BOV_A0754| BCAN_B0818, NikA |
| OPN    |        |           |                   | IM   | BMEII0488, nikB| BruAb20429, nikB | BRA0802, nikC | BOV_A0752, NikB | |
| OPN    |        |           |                   | IM   | BMEII0489, nikC| BruAb20430, nikV | BRA0803, nikB | BCAN_B0816, NikC | |
| OPN    |        |           |                   | ABC  | BMEII0490, nikD| BruAb20431, nikD | BRA0800, nikE | BOV_A0751, NikD | |
| OPN    |        |           |                   | ABC  | BMEII0491, nikE| BruAb20432, nikE | BRA0801, nikD | BCAN_B0814, NikE | |
| 71     | OPN    |           | Oligopeptide import| BP   | BMEII0504      | BruAb20446 | BRA0783| BOV_A0737| BCAN_B0800 |
| OPN    |        |           |                   | IM   | BMEII0505      | BruAb20447 | BRA0788| BOV_A0736| BCAN_B0799 |
| OPN    |        |           |                   | IM   | BMEII0506      | BruAb20448 | BRA0787| BOV_A0735| BCAN_B0798 |
| OPN    |        |           |                   | ABC  | BMEII0507      | BruAb20449 | BRA0786| BOV_A0734| BCAN_B0797 |
| OPN    |        |           |                   | ABC  | BMEII0508      | BruAb20450 | BRA0785|         | BCAN_B0796 |
| 72     | OPN    |           | Oligopeptide import| BP   | BMEII0691      | BruAb20648 | BRA0576| BOV_A0542|           |
| OPN    |        |           |                   | BP   | BMEII0734      | BruAb20684 | BRA0538| BOV_A0468| BCAN_B0538 |
| OPN    |        |           |                   | BP   | BMEII0735, oppA | BruAb20685 | BRA0537| BOV_A0467| BCAN_B0537 |
| OPN    |        |           |                   | IM   | BMEII0736      | BruAb20686 | BRA0536| BOV_A0466| BCAN_B0535 |
| OPN    |        |           |                   | IM   | BMEII0737      | BruAb20687 | BRA0535| BOV_A0465| BCAN_B0536 |
| OPN    |        |           |                   | ABC2 | BMEII0738      | BruAb20688 | BRA0534| BOV_A0464| BCAN_B0534 |
| 73     | OPN    |           | Oligopeptide import| BP   | BMEII0859      | BruAb20792 | BRA0490| BOV_A0352| BCAN_B0412 |
| OPN    |        |           |                   | IM   | BMEII0860      | BruAb20794 | BRA0488| BOV_A0351| BCAN_B0411 |
| OPN    |        |           |                   | IM   | BMEII0861      | BruAb20794 | BRA0497| BOV_A0350| BCAN_B0410 |
| OPN    |        |           |                   | ABC  | BMEII0863      | BruAb20796 | BRA0495| BOV_A0347| BCAN_B0408 |
| OPN    |        |           |                   | ABC  | BMEII0864      | BruAb20797 | BRA0404| BOV_A0348| BCAN_B0407 |

Table 1: Continued.
| Number | Family | Subfamily | Substrate/Function | Type | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|--------|--------|-----------|-------------------|------|---------------|------------|--------|--------|--------|
| 75     | OSP    |           | Maltose import    | ABC  | BMEI1713, malK | BruAb10233 | BR0238 | BOV,0231 | BCAN,A0241 |
|        | OSP    |           | Maltose import    | IM   | BMEI1714, malG | BruAb10231 | BR0237 | BOV,0230 | BCAN,A0240 |
|        | OSP    |           | Maltose import    | IM   | BMEI1715, malF | BruAb10232 | BR0236 | BOV,0229 | BCAN,A0239 |
|        | OSP    |           | Maltose import    | BP   | BMEI1716      | BruAb10230 | BR0235 | BOV,0228 | BCAN,A0238 |
| 76     | OSP    |           | Oligosaccharide or polyol import | ABC  | BMEI1712, ugpC | BruAb21119 | BRA1183 | BOV,A1086 | BCAN,B1214 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI1713, ugpA | BruAb21118 | BRA1181 | BOV,A1085 | BCAN,B1213 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI1714, ugpE | BruAb21117 | BRA1182 | BOV,A1084 | BCAN,B1212 |
|        | OSP    |           | Oligosaccharide or polyol import | BP   | BMEI1715      | BruAb21116 | BRA1180 | BOV        | BCAN,B1211 |
| 77     | OSP    |           | Oligosaccharide or polyol import | ABC  | BMEI1716      | BruAb20483 | BRA0749 | BOV,A0700 | BCAN,B0757 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI1717      | BruAb20484 | BRA0748 | BOV,A0701 | BCAN,B0755 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI1718      | BruAb20485 | BRA0747 | BOV        | BCAN,B0753 |
|        | OSP    |           | Oligosaccharide or polyol import | BP   | BMEI1719      | BruAb20486 | BRA0746 | BOV        | BCAN,B0751 |
|        | OSP    |           | Oligosaccharide or polyol import | ABC  | BMEI1720      | BruAb20487 | BRA0745 | BOV        | BCAN,B0749 |
| 78     | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI1721      | BruAb20537 | BRA0693 | BOV,A0648 | BCAN,B0691 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI1722      | BruAb20538 | BRA0692 | BOV,A0646 | BCAN,B0689 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI1723      | BruAb20539 | BRA0691 | BOV,A0645 | BCAN,B0687 |
| 79     | OSP    |           | SN-glycerol-3-phosphate import | ABC  | BMEI0621, ugpC | BruAb20568, ugpC | BRA0658, ugpC | BOV,A0620 | BCAN,B0658 |
|        | OSP    |           | SN-glycerol-3-phosphate import | IM   | BMEI0622, ugpE | BruAb20569, ugpE | BRA0657, ugpE | BOV,A0619 | BCAN,B0657 |
|        | OSP    |           | SN-glycerol-3-phosphate import | IM   | BMEI0623, ugpE | BruAb20570, ugpA | BRA0656, ugpA | BOV,A0618 | BCAN,B0656 |
|        | OSP    |           | SN-glycerol-3-phosphate import | IM   | BMEI0624, ugpA | BruAb20571, ugpA | BRA0655, ugpA | BOV,A0617 | BCAN,B0655 |
| 80     | OSP    |           | Oligosaccharide or polyol import | ABC  | BMEI0625      | BruAb20702 | BRA0521 | BOV,A0545 | BCAN,B0520 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI0626      | BruAb20704 | BRA0519 | BOV,A0542 | BCAN,B0518 |
|        | OSP    |           | Oligosaccharide or polyol import | IM   | BMEI0627      | BruAb20705 | BRA0518 | BOV,A0541 | BCAN,B0517 |
|        | OSP    |           | Oligosaccharide or polyol import | BP   | BMEI0628      | BruAb20706 | BRA0516 | BOV,A0449 | BCAN,B0516 |
|        | OSP    |           | Oligosaccharide or polyol import | BP   | BMEI0629      | BruAb20707 | BRA0515 | BOV        | BCAN,B0515 |
| 81     | OSP    |           | Maltose import    | ABC  | BMEI0940      | BruAb20874 | BRA0307 | BOV,A0282 | BCAN,B0308 |
|        | OSP    |           | Maltose import    | IM   | BMEI0942      | BruAb20875 | BRA0306 | BOV,A0281 | BCAN,B0307 |
|        | OSP    |           | Maltose import    | IM   | BMEI0943      | BruAb20876 | BRA0305 | BOV,A0280 | BCAN,B0306 |
|        | OSP    |           | Maltose import    | BP   | BMEI0944      | BruAb20877 | BRA0304 | BOV        | BCAN,B0305 |
| 82     | OTCN   |           | Glycine betaine/L-proline import | ABC  | BMEI0439, proV | BruAb11568 | BRI181 | BOV,A1526 | BCAN,A1616 |
|        | OTCN   |           | Glycine betaine/L-proline import | IM   | BMEI0440, proW | BruAb11567 | BRI180 | BOV,A1525 | BCAN,A1615 |
|        | OTCN   |           | Glycine betaine/L-proline import | BP   | BMEI0441, proX | BruAb11566 | BRI179 | BOV,A1524 | BCAN,A1614 |
| 83     | OTCN   |           | Choline S-dependent regulation of yehZYXW | BP   | BMEI1725 | BruAb10220 | BRA0225 | BOV,A0216 | BCAN,A0228 |
|        | OTCN   |           | Choline S-dependent regulation of yehZYXW | IM   | BMEI1726, proW | BruAb10217 | BRA0222 | BOV,A0215 | BCAN,A0227 |
|        | OTCN   |           | Choline S-dependent regulation of yehZYXW | IM   | BMEI1728, proW | BruAb10219 | BRA0224 | BOV,A0223 | BCAN,A0225 |
|        | OTCN   |           | Choline S-dependent regulation of yehZYXW | ABC  | BMEI1727, proV | BruAb10218 | BRA0223 | BOV,A0224 | BCAN,A0226 |
| 84     | OTCN   |           | Osmoprotectants, Taurine, Cyanate & Nitrate | BP   | BMEI1737 | BruAb10207 | BRA0211 | BOV,A0204 | BCAN,A0215 |
|        | OTCN   |           | Osmoprotectants, Taurine, Cyanate & Nitrate | IM   | BMEI1739 | BruAb10206 | BRA0213 | BOV,A0202 | BCAN,A0213 |
|        | OTCN   |           | Osmoprotectants, Taurine, Cyanate & Nitrate | ABC  | BMEI1008, tauB | BruAb21123 | BRA1187 | BOV,A0190 | BCAN,B1217 |
| 85     | OTCN   |           | Taurine import    | BP   | BMEI1009 | BruAb21122 | BRA1186 | BOV,A1089 | BCAN,B1218 |
|        | OTCN   |           | Taurine import    | IM   | BMEI1007, tauC | BruAb21124 | BRA1188 | BOV,A1091 | BCAN,B1219 |
|        | OTCN   |           | Taurine import    | ABC  | BMEI1008, tauB | BruAb21123 | BRA1187 | BOV,A1090 | BCAN,B1217 |
| Number | Family | Subfamily | Substrate/Function | Type | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|--------|--------|-----------|-------------------|------|--------------|-----------|--------|--------|--------|
| 86     | OTCN   |           | Glycine betaine/L-proline import | ABC  | BMEII0548    | BruAb20492 | BRA0740 | BOV_A0692 | BCAN_B0748 |
|        | OTCN   |           | Glycine betaine/L-proline import | IM   | BMEII0549    | BruAb20493 | BRA0739 | BOV_A0691 | BCAN_B0747 |
|        | OTCN   |           | Glycine betaine/L-proline import | BP   | BMEII0550    | BruAb20494 | BRA0738 | BOV_A0690 | BCAN_B0746 |
| 87     | OTCN   |           | Nitrate import | BP   | BMEII0797    | BruAb20753 | BRA0469 | BOV_A0406 | BCAN_B0741 |
|        | OTCN   |           | Nitrate import | ABC  | BMEII0798, nrtC | BruAb20755 | BRA0467 | BOV_A0407 | BCAN_B0740 |
|        | OTCN   |           | Nitrate import | IM   | BMEII0799, nrtB | BruAb20755 | BRA0468 | BOV_A0408 | BCAN_B0469 |
| 88     | OTCN   |           | Taurine import | ABC  | BMEII0961    | BruAb10894 | BRA0286 | BOV_A0262 | BCAN_B0288 |
|        | OTCN   |           | Taurine import | IM   | BMEII0962    | BruAb10895 | BRA0285 | BOV_A0261 | BCAN_B0287 |
|        | OTCN   |           | Taurine import | BP   | BMEII0963    | BruAb10896 | BRA0284 | BOV_A0260 | BCAN_B0286 |
| 89     | PAO    |           | Polar amino acid import | ABC  | BMEI0108     | BruAb1932  | BR1959  | BOV_A0336 | BCAN_A2004 |
|        | PAO    |           | Polar amino acid import | ABC  | BMEI0111     | BruAb1935  | BR1956  | BOV_A1885 | BCAN_A2001 |
|        | PAO    |           | Polar amino acid import | IM   | BMEI0112     | BruAb1931  | BR1955  | BOV_A1882 | BCAN_A2000 |
|        | PAO    |           | Polar amino acid import | IM   | BMEI0113     | BruAb1930  | BR1954  | BOV_A1081 | BCAN_A1999 |
|        | PAO    |           | Polar amino acid import | BP   | BMEI0114     | BruAb1929  | BR1953  | BOV_A1880 | BCAN_A1998 |
| 90     | PAO    |           | Arginine/Ornithine binding precursor | BP   | BMEI1022     | BruAb20595 | BRA0632 | BOV_A0593 | BCAN_A0967 |
|        | PAO    |           | Arginine/Ornithine binding precursor | BP   | BMEI1022     | BruAb20595 | BRA0632 | BOV_A0593 | BCAN_A0967 |
|        | PAO    |           | Arginine/Ornithine binding precursor | BP   | BMEI1022     | BruAb20595 | BRA0632 | BOV_A0593 | BCAN_A0967 |
| 91     | PAO    |           | General L-amino acid import | ABC  | BMEI1208, appP | BruAb10762 | BRA0745 | BOV_A0890 | BCAN_A0760 |
|        | PAO    |           | General L-amino acid import | IM   | BMEI1209, appM | BruAb10758 | BRA0744 | BOV_A0739 | BCAN_A0759 |
|        | PAO    |           | General L-amino acid import | IM   | BMEI1210, appQ | BruAb10760 | BRA0743 | BOV_A0737 | BCAN_A0758 |
|        | PAO    |           | General L-amino acid import | BP   | BMEI1211, appJ | BruAb10761 | BRA0741 | BOV_A0738 | BCAN_A0756 |
|        | PAO    |           | General L-amino acid import | BP   | BMEI0349, appJ | BruAb20285 | BRA0948 | BOV_A0736 | BCAN_B0969 |
| 92     | PAO    |           | Arginine | BP   | BMEI1627     | BruAb10321 | BR2095  | BOV_A0308 | |
| 93     | PAO    |           | Cystine import | ABC  | BMEI0599    | BruAb20545 | BRA0684  | BOV_A0640 | BCAN_B0682 |
|        | PAO    |           | Cystine import | IM   | BMEI0600    | BruAb20546 | BRA0683  | BOV_A0639 | BCAN_B0681 |
|        | PAO    |           | Cystine import | BP   | BMEI0601    | BruAb20547, fliY | BRA0682, fliY | BOV_A0638, fliY | BCAN_B0680 |
| 94     | PAO    |           | Polar amino acid import | IM   | BMEI1104    | BruAb1052  | BR0953  | BCAN_A0965 | |
| 95     | PAO    |           | Polar amino acid import | IM   | BMEI1104    | BruAb1052  | BR1056  | BCAN_A0965 | |
| 96     | UVR    |           | DNA repair | ABC2 | BMEI0878    | BruAb1110, UvrA | UvrA | BOV_A1063 | BCAN_A1124 |
| 97     | YHBG   |           | Possible LPS transport to outer membrane | ABC  | BMEI1790    | BruAb10153 | BR157  | BOV_A0152 | BCAN_A0162 |
|        | YHBG   |           | Possible LPS transport to outer membrane | SS   | BMEI1791    | BruAb10152 | BR156  | BOV_A0151 | BCAN_A0161 |

ABC: ATP-Binding Cassette; IM: Inner membrane protein; BP: Binding protein; IM-ABC: Inner membrane protein-ATP binding cassette fusion; ABC2: 2 ABC proteins fused together; OMP: Outer membrane protein; MFP: Membrane fusion protein; SS: Signal sequence; LPP: Extracytoplasmic protein with a lipoprotein type signal sequence; BM: Brucella melitensis; BA: Brucella abortus; BS: Brucella suis; Bold Text: Indicates a frame shift mutation or premature stop codon in these genes.
Table 2: ABC system families/subfamilies.

| Family                        | Name                                                                 | Subfamily | Description and Function                                                                 |
|-------------------------------|----------------------------------------------------------------------|-----------|------------------------------------------------------------------------------------------|
| Exporters (predicted and experimental) |                                                                      |           |                                                                                           |
| DPL, Drugs, Peptides, Lipids  | HMT                                                                |           | Mitochondrial and bacterial transporters II                                              |
|                               | CHV                                                                |           | Beta(1–2) Glucan export                                                                  |
|                               | MDL                                                                |           | Mitochondrial and bacterial transporters I                                              |
|                               | LIP                                                                |           | Lipid A or glycerophospholipid export                                                    |
|                               | PRT                                                                |           | Proteases, Lipases, S-Layer protein export                                               |
|                               | CYD                                                                |           | Cytochrome bd biogenesis                                                                 |
|                               | CCM                                                                |           | Cytochrome C biogenesis                                                                 |
|                               | CLS                                                                |           | Capsular polysaccharide, lipopolysaccharide and teichoic acids                           |
|                               | FAE                                                                |           | Fatty Acid Export                                                                        |
| Importers                     |                                                                      |           |                                                                                           |
| DLM                           | D- L-Methionine and derivatives                                     |           |                                                                                           |
| CBY                           | CBU                                                                |           | Related to MOI family but unknown substrate                                              |
| MKL                           | YHBG                                                               |           | Related to HAA family, but unknown substrate                                            |
| CDI                           |                                                                    |           | Cell division                                                                             |
| MET                           |                                                                    |           | Metals                                                                                   |
| MOS                           |                                                                    |           | Monosaccharides                                                                          |
| MOI                           |                                                                    |           | Mineral and Organic ions                                                                 |
| PAO                           |                                                                    |           | Polar amino acids and Opines                                                              |
| HAA                           | OSP                                                                |           | Hydrophobic amino acids and amides                                                        |
|                               | OPN                                                                |           | Oligosaccharides and polyols                                                             |
|                               | OTCN                                                               |           | Osmoprotectants Taurine Cyanate and Nitrate                                               |
|                               | ISVH                                                               |           | Iron-Siderophores VitaminB-12 and Hemin                                                   |
|                               |                                                                    |           |                                                                                           |
| Isolated cellular process     | ISB                                                                |           | Iron-sulphur centre biogenesis                                                            |
|                               | ART, Antibiotic resistance and translation regulation               | REG       | Translation regulation                                                                    |
|                               | UVR                                                                |           | DNA repair and drug resistance                                                           |
|                               |                                                                    |           |                                                                                           |
| Unknown                       | DRI                                                                | YHH       | Drug resistance, putative                                                                 |
|                               |                                                                    |           | Possible nitrous oxide reduction                                                         |
|                               | NO                                                                 | NOS       | Unclassified Systems                                                                     |
|                               | o228                                                               |           | Unknown                                                                                   |

Two predicted erythritol transport systems have been reported that have yet to be confirmed by experimental data [8, 43]. Although the erythritol transporter identified in this study has also been identified by Crasta et al. [43], it should be noted that B. abortus S19 has this transport system inactivated by pseudogenes and yet it is still able to incorporate erythritol [43], indicating that this ABC system might not be wholly responsible for erythritol transport. Another study has demonstrated that B. ovis does not utilise erythritol as readily as other sugars [44].

In this study we have identified one ABC system in BM that we have categorised within a new ABC system family (currently labelled NEW1; See Table 1). This system includes BP and IM proteins related to those of the MOS family and ABC proteins that are different to those from the MOS family. We previously identified a similar ABC system in the genomes of Burkholderia pseudomallei and Burkholderia mallei strains [45]. Clearly, experimental data is required to define the function of this system.

5. Differences between Brucella Species

Although there is similarity between the ABC system inventories of the Brucella strains studied in this work, we have identified systems that are absent in one or several Brucella species (Table 4). The systems that are absent from species are not critical for bacterial survival but could contribute to differences in the lifestyles or virulence of the Brucella species. Our data shows that there are ABC systems absent from all of the Brucella strains studied. In particular, BO (5 systems), BC (4 systems), and BA (4 systems) lack systems that are present in BM and/or BS. The absence of
Table 3: Brucella ABC import ability.

| Substrate                                | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|------------------------------------------|---------------|------------|---------|---------|---------|
| Branch chain amino acids                 | ** ** **      | ** **      | ** **   | **      | ** **   |
| Iron (III)                               | ** ** **      | ** **      | ** **   | ** ** **| ** ** **|
| Cobalt                                   | *             | *          | *       | *       | *       |
| Zinc                                     | *             | *          | *       | *       | *       |
| Thiamine                                 | *             | *          | *       | —       | *       |
| Putrescine                               | ** ** **      | ** **      | **      | —       | **      |
| Sulphate                                 | ** ** **      | ** **      | **      | **      | **      |
| Phosphate                                | *             | *          | *       | *       | *       |
| Molybdenium                              | *             | *          | *       | —       | *       |
| Spermidine                               | ** ** **      | ** **      | **      | —       | **      |
| Ribose                                   | ** ** **      | ** **      | ** **   | ** ** **| ** ** **|
| Galactoside                              | —             | ** **      | ** **   | **      | **      |
| Xylose                                   | *             | *          | *       | —       | *       |
| Erythritol                               | *             | *          | *       | —       | *       |
| Dipeptides                               | ** ** **      | ** **      | **      | **      | **      |
| Oligopeptides                            | **** ** ****  | **** ** **** | ** **   | ** ** **| ** ** **|
| Nickel                                   | *             | —          | *       | —       | *       |
| Maltose                                  | *             | *          | *       | *       | *       |
| Oligosaccharide or polyol                | ** ** **      | *          | **      | ** ** **| ** ** **|
| SN-glycerol-3-phosphate                  | *             | *          | *       | —       | —       |
| Taurine                                  | ** ** **      | ** **      | **      | *       | **      |
| Glycine betaine                          | *             | —          | *       | —       | *       |
| Nitrate                                  | *             | *          | *       | *       | *       |
| Polar amino acids                        | —             | —          | —       | *       | *       |
| Cystine                                  | *             | *          | *       | *       | *       |
| General L amino acids                    | *             | —          | *       | *       | *       |

This table does not include any ABC system with pseudogenes present. ** ** ** > 5 functional systems, ** ** > 3 or 4 functional systems, ** ** > 2 functional systems, * > 1 functional system, — No functional systems.
Table 4: ABC system genes absent in at least one species when compared to B. melitensis.

| Number | Family | Subfamily | Substrate/Function | Type | B. melitensis | B. abortus | B. suis | B. ovis | B. canis |
|--------|--------|-----------|--------------------|------|---------------|------------|--------|---------|---------|
| 5      | CCM    |           | Possibly heme export | IM   | BMEI1851      | –          | +      | +       | +       |
|        |        |           |                    | IM   | BMEI1852      | –          | +      | +       | +       |
|        |        |           |                    | ABC  | BMEI1853      | –          | +      | +       | +       |
| 6      | CDI    |           | Involved in cell division | IM   | BMEI0073, ftsX | +          | +      | –       | +       |
|        |        |           |                    | ABC  | BMEI0072, ftsE | +          | +      | –       | +       |
| 7      | CLS    |           | O antigen export system | ABC  | BMEI1416, rfbB | –          | +      | +       | +       |
|        |        |           |                    | IM   | BMEI1415, rfbD | –          | +      | +       | +       |
| 13     | DPL    | PRT       | Fatty acid export   | IM-ABC | BMEI0984     | +          |          | –       | +       |
| 14     | DPL    | CHV       | Beta-(1 → 2) glucan export | IM-ABC | BMEI0976     | +          | –      | +       | +       |
| 16     | DPL    | HMT       | Involved in mitochondrial export systems | IM-ABC | BMEI1743     | –          | –      | –       | –       |
| 22     | FAE    |           | Iron/sulphur centre biogenesis | CYTP | BMEI1042    | +          |          | +       | –       |
| 31     | ISB (ABCX) |       |                    | CYTP | BMEI1042     | +          |          | +       | –       |
|        |        |           |                    | ABC  | BMEI1041      | +          | –      | +       | –       |
|        |        |           |                    | ABC  | BMEI0964      | +          | +      | –       | –       |
| 36     | MKL    |           | Involved in toluene tolerance | IM   | BMEI0965, ttg2B | +          | +      | +       | –       |
|        |        |           |                    | SS   | BMEI0963, ttg2C |          | +      | +       | –       |
|        |        |           |                    | IM   | BMEI0087      | +          | +      | +       | –       |
| 60     | o228   |          | Unknown             | ABC  | BMEI0359      | –          | –      | –       | –       |
|        |        |           |                    | IM   | BMEI0360      | –          | –      | –       | –       |
|        |        |           |                    | IM   | –             | BruAb10085 | +      |          | –       |
| 61     | o228   | Unknown   | MFP                 | IM-ABC | –           | $          | $      | –       | –       |
|        |        |           |                    | ABC  | –             | BruAb10084 | +      | +       | –       |
| 62     | o228   | Unknown   | MFP                 | IM-ABC | –           | $          | $      | –       | –       |

Excludes ABC systems involved in import; –: gene absent in the Brucella species; +: gene present in the Brucella species; $: pseudogene present in the Brucella species; Number: refers to ABC system number in the full inventories/alignments of Brucella ABC systems.

The ISB (formally ABCX) system from BO and BC is an interesting observation since the ISB systems are soluble complexes involved in labile [Fe-S] biogenesis, which is important in resistance to oxidative stresses. This could indicate that B. ovis and B. canis reside in environments that are low in oxygen or high in oxygen reductants, or that they lack enzymes that need labile [Fe-S] centres [46, 47]. Furthermore, this difference may be a factor contributing to the reduced virulence for humans of B. ovis and B. canis when compared to B. melitensis, B. suis, and B. abortus. The CDI system absent from B. ovis is comprised of two proteins, FtsE (ABC protein) and FtsX (IM protein) [48], and has been studied in E. coli and other bacteria including Bacillus subtilis [49] and Mycobacterium tuberculosis [50]. This CDI system is involved in cell division. E. coli mutants of ftsE show a reduced growth capacity [51]. The MKL system absent from BC may play a role in toluene tolerance, since Tn5 insertions within the ttgA2 gene coding for the MKL ABC protein in
Suis Thomsen. Compiling ABC systems inventories of these strains may identify further differences which may have biological relevance. Among the newly sequenced Brucella species, it is widely accepted that the three species that may cause the most human brucellosis are B. melitensis, B. suis, and B. abortus (and occasionally B. canis). This study has shown that these four species of Brucella have a larger set of ABC systems encoded within their genomes than B. ovis, which is not known to cause human disease. Although it is difficult to ascertain the exact effect of the loss of these ABC systems on B. ovis, it is possible to hypothesise that, along with other genetic differences observed [15], they contribute to its overall reduced virulence in humans. It should also be noted there that four further Brucella strains have been genome sequenced since this work was completed: B. melitensis 63/9, B. abortus 2308, B. abortus S19, and B. suis Thomsen. Compiling ABC systems inventories of these strains may identify further differences between strains that may have biological relevance. Among the newly sequenced strains are B. suis Thomsen, a strain which is not known to cause disease in humans, and B. abortus S19, a vaccine strain. ABC system inventories of these strains would be of particular interest since they are considered less pathogenic than the wild-type strains and yet the reasons for this lack of pathogenicity are currently unknown. Overall, the identified differences observed in the ABC system inventory of the Brucella strains studied should contribute to a greater understanding of differences in the lifestyles of the Brucella species.

6. Conclusions

In this study the ABC systems of B. melitensis strain 16 M, B. suis strain 1330, B. abortus 9-941, B. canis strain RM6/66, and B. ovis strain 63/290 have been reannotated using the ABCISSE database in order to provide a new and improved set of annotated Brucella ABC systems for the strains studied. The information obtained and the uniform annotation and classification of ABC systems in these closely related species has enabled a more detailed analysis of the roles of ABC systems in Brucella species, contributing to an improved understanding of Brucella lifestyle and pathogenicity. Previous analysis of the Brucella genomes has shown that there is over 90% genome similarity between the Brucella species [13, 14]. Similarly, the ABC system inventory compiled in this work reflects the close similarities of the Brucella species. However, despite the high genetic homology of Brucella, classification of ABC systems in these closely related species has enabled a more detailed analysis of the roles of ABC systems encoded within their genomes than Brucella species. It is of particular interest since they are considered less pathogenic than other genetic differences observed [15, 16].

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