The controversial nature of the Weissella genus: technological and functional aspects versus whole genome analysis-based pathogenic potential for their application in food and health

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Despite the use of several Weissella (W.) strains for biotechnological and probiotic purposes, certain species of this genus were found to act as opportunistic pathogens, while strains of W. ceti were recognized to be pathogenic for farmed rainbow trout. Herein, we investigated the pathogenic potential of weissellas based on in silico analyses of the 13 whole genome sequences available to date in the NCBI database. Our screening allowed us to find several virulence determinants such as collagen adhesins, aggregation substances, mucus-binding proteins, and hemolysins in some species. Moreover, we detected several antibiotic resistance-encoding genes, whose presence could increase the potential pathogenicity of some strains, but should not be regarded as an excluding trait for beneficial weissellas, as long as these genes are not present on mobile genetic elements. Thus, selection of weissellas intended to be used as starters or for biotechnological or probiotic purposes should be investigated regarding their safety aspects on a strain to strain basis, preferably also by genome sequencing, since nucleotide sequence heterogeneity in virulence and antibiotic resistance genes makes PCR-based screening unreliable for safety assessments. In this sense, the application of W. confusa and W. cibaria strains as starter cultures or as probiotics should be approached with caution, by carefully selecting strains that lack pathogenic potential.

Keywords: Weissella, in silico analysis, genome, virulence, antibiotic resistance

INTRODUCTION

Weissella species are non-spore forming, catalase-negative and Gram-positive bacteria that are non-motile, with the exception of Weissella (W.) beninensis. To date, the Weissella genus comprises 19 validly described species (February 2015\(^1\)). Most of these were isolated from and associated with fermented foods, e.g., W. confusa, W. cibaria (Björkroth et al., 2002), W. kimchii (Choi et al., 2002),

\(^1\)http://www.bacterio.net
**RESULTS AND DISCUSSION**

**Virulence Determinants in Weissella**

The safety of many LAB species have been recognized as GRAS (Generally Regarded As Safe; for the USA; Food and Drug Administration, 1999) or have attained the QPS (Qualified Presumption of Safety; for the European Commission; European Food Safety Authority (EFSA), 2004) status. Indeed, many people refer to these bacteria as being innocuous, and even associated with health beneficial properties. However, it is well known that certain species within a genus, or even certain strains within a specific species, may have different health impacts, as has been pointed out for the enterococci (Franz et al., 2003; Ogier and Serror, 2008). So far, no Weissella species have QPS status (European Food Safety Authority (EFSA), 2015) Data on virulence factors present in Weissella species are quite scarce, and genomic analysis can therefore aid in detecting and describing the occurrence of virulence determinants that may be present at species or strain level within this genus. In this regard, Ladner et al. (2013) found in the genome sequence of W. ceti NC36, an emerging pathogen of farmed rainbow trout in the United States, the presence of several putative virulence factor genes, which did not have homologs encoded in any of the other sequenced Weissella genomes. In particular, these include five collagen adhesin genes (WCNC_00912, WCNC_00917, WCNC_00922, WCNC_05547, and WCNC_06207), a platelet-associated adhesin gene (WCNC_01820) and a gene for a mucus-binding protein (WCNC_01840; Ladner et al., 2013). The five collagen adhesin genes included those from W. ceti WS105 (three collagen adhesins), W. ceti WS74 (three collagen adhesins), W. ceti WS08 (three collagen adhesins), W. ceti WS08

**MATERIALS AND METHODS**

**Data Sequences**

Data sequences of genomes of the 13 strains belonging to nine Weissella species (Table 1) were retrieved from the National Centre for Biotechnology Information (NCBI\(^2\); accessed on February, 2015). All genome sequences available were analyzed for the presence of different virulence determinants (aggregation substances, adhesins, toxins, pili, hemolysins) and of antibiotic resistance genes, such as fosfomycin and methicillin resistance genes. The accession numbers of each target gene sequence are indicated in Tables 1–3 and Figures 1–5.

**Phylogenetic Analyses**

All selected target genes were subjected to phylogenetic analyses to determine phylogenetic relationships with those of closely related genera. Alignment of sequences was done using the CLUSTAL W module of the Lasergene program, version 5.05 (MegAlign, Inc., Madison, WI, USA). Phylogenetic trees were reconstructed by the maximum parsimony method using MegAlign (Lasergene program, version 5.05).

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1. **Collagen adhesins**, 2. **Qualified Presumption of Safety**

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**In silico analyses of Weissella pathogenicity**

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(two collagen adhesins), and W. confusa LBAE C39-2 (one collagen adhesion; Table 2). DNA sequences coding for collagen adhesion proteins in Weissella spp. and other LAB (Leuconostoc “Ln.”, Lactococcus “Lc.”, Enterococcus “E.”, and Lactobacillus “Lb.”) were aligned using CLUSTAL W of the Lasergene program, version 5.05 (MegAlign, Inc., Madison, WI, USA) and the most parsimonious phylogenetic tree was reconstructed. The dendrogram generated showed four groups (Figure 1). The first group contained two of the three collagen adhesion genes found in W. ceti strains, E. faecalis, Leuconostoc and Lactococcus, while genes for group II collagen adhesins were only present in W. ceti NC36 and Lb. delbrueckii. The third group presented the genes for the third collagen produced by W. ceti strains. In the last group (group IV) E. faecium and Leuconostoc collagen adhesion genes clustered together, however a W. confusa LBAE C39-2 collagen adhesin gene also formed a single lineage (Figure 1). In general, the close relatedness of Weissella, Enterococcus, and Leuconostoc collagen adhesion genes at the level of the primary protein sequence may suggest the same evolutionary origin of these proteins in these bacteria. Further genome sequencing of other Weissella species would be required to analyze this relatedness with enterococci and leuconostocs in more depth. The presence of virulence determinants commonly present in enterococci also in weissellas and leuconostocs may suggest a horizontal gene transfer event from the Enterococcus genus, the latter of which indeed includes strains that are commonly present in many different habitats (Franz et al., 2003).

The role of the genes above in the virulence of Weissella is still unknown. Further studies are needed to confirm whether these virulence genes are expressed or not, and if they are located
TABLE 2 | Potential virulence genes of Weissella species as revealed by in silico screening of the annotated genome sequences.

| Strains | Aggregation substance | Collagen adhesion | Hemolysin | Mucus-binding proteins | Staphylococcal surface protein |
|---------|-----------------------|-------------------|-----------|------------------------|--------------------------------|
|         |                       |                   |           |                        |                                |
| W. ceti WS08 | –                     | 2 CA (WS08_0071, WS08_0073) | 1 Hly (WS08_0075), 1 HlyA (WS08_0092) | –                       | SSPA (WS08_0030, WS08_0040, WS08_0045, WS08_0097, WS08_1166, WS08_1190) |
| W. ceti WS74 | –                     | 3 CA (WS74_0069, WS74_0070, WS74_0084) | 1 Hly (WS74_0057), 1 HlyA (WS74_0068) | –                       | 4 SPA (WS74_0030, WS74_0040, WS74_0045, WS74_1225, WS74_1261) |
| W. ceti WS105 | –                     | 3 CA (WS105_0070, WS105_0071, WS105_0081) | 1 Hly (WS105_0054), 1 HlyA (WS105_0065), 1 Hly-like protein (WS105_0022) | –                       | 4 SPA (WS105_0030, WS105_0040, WS105_1219, WS105_1255) |
| W. ceti NC36 | –                     | 6 CA (WCNC_00912, WCNC_00917, WCNC_00922, WCNC_00947, WCNC_06207) 1 PA-ADHE | –                       | 1 MBP (WCNC_01840) | –                       |
| W. cibaria KACC 11862 | –                     | –                 | 2 Hly (ESE_RS0108795, ESE_RS11605) | –                       | –                       |
| W. confusa LBAE C39-2 | –                     | 1 (WEISSC39_RS00260) | 2 Hly (WEISSC39_RS008935, WEISSC39_RS00940) | –                       | 1 MBP (WEISSC39_RS05980)                    |
| W. halotolerans DSM 20190 | –                     | –                 | 2 Hly (G414_RS0108795, G414_RS0108810) | –                       | –                       |
| W. hellenica Wikimi14 | –                     | –                 | 2 Hly (TY24_RS08990, TY24_RS08995) | –                       | –                       |
| W. koreensis KACC 15510 | –                     | –                 | –                       | –                       | –                       |
| W. koreensis KCTC 3621 | –                     | –                 | –                       | –                       | –                       |
| W. oryzae SG25 | 2 AGS (WOSG25_000030, WOSG25_000040) 2 Asa1/PrgB (WOSG25_000030, WOSG25_000040) | 3 hemolysins (WOSG25_050280, WOSG25_050285, WOSG25_050290, WOSG25_050295) | –                       | –                       | –                       |
| W. paramesenteroides ATCC 33313 | –                     | –                 | 2 Hly (HMPREF0877_RS00966, HMPREF0877_RS009670) | –                       | –                       |
| W. thailandensis fsh4-2 | –                     | –                 | 2 Hly (WT2_001519, WT2_001520) | –                       | –                       |

on mobile genetic elements (e.g., transposons). However, the collagen adhesin protein (Ace) in Enterococcus was reported to be involved in adhesion to collagen and to contribute to infective endocarditis and urinary tract infection (Aymerich et al., 2006; Nallapareddy et al., 2011). In addition, the common localization of this gene on plasmids or transposon may pose a risk related with horizontal gene transfer to pathogenic bacteria. On the other hand, adherence is an important pre-requisite for the colonization of probiotics, providing a competitive advantage in different ecosystems. The presence of adhesin genes in weissellas that are not located on mobile genetic elements, and which are not transferable, should therefore not negatively reflect on the strains probiotic potential, and should not be an excluding factor for its use. It could be regarded as a key factor for the attachment of probiotic bacterial cell in the human host, and thus could be regarded as a colonization factor rather than a virulence factor (Dunne et al., 2004).

In silico analyses of Weissella genomes also showed the presence of genes coding for two unnamed aggregation substances (WOSG25_050600 and WOSG25_190240) as well as two aggregation substances named Asa1/PrgB (WOSG25_200030 and WOSG25_200040) in W. oryzae SG25 (Table 2). The sequences of the genes encoding the unnamed aggregation substances, the aggregation substances Asa1/PrgB from W. oryzae SG25 and...
those of other LAB (Leuconostoc and Enterococcus) were aligned using the CLUSTAL W of Lasergene program, and the most parsimonious phylogenetic tree was constructed. The results obtained showed that the aggregation substance genes found in W. oryzae SG25 clustered with those of Ln. pseudomesenteroides and E. faecalis (group I in dendrogram), the latter being the aggregation substance gene of E. faecalis pMG2200, which is located on a plasmid. This suggests that horizontal gene transfer from E. faecalis to other LAB such as Weissella and Leuconostoc (Figure 2A) probably occurred. Other aggregation substance genes of different strains of E. faecalis, Ln. mesenteroides, and Ln. pseudomesenteroides were very divergent, forming several clusters (Figure 2A). When aggregation substance gene sequences of Asa1/PrgB from W. oryzae SG25, E. faecalis, and Ln. pseudomesenteroides were clustered, the dendrogram showed aggregation substances Asa1/PrgB coding genes from W. oryzae SG25 and E. faecalis or Leuconostoc (Group I) to cluster very closely, also suggesting a horizontal gene transfer between these bacteria (Figure 2B). The presence of an asa1 gene was also reported in other potential probiotic LAB, such as Lb. casei SJRP35, Ln. citreum SJRP44, and Ln. mesenteroides subsp. mesenteroides SJRP58 isolated from Water-Buffalo Mozzarella.
Cheese (Jeronymo-Ceneviva et al., 2014), and also in Lc. lactis subsp. Lactis KT2W2L (Hwanhlem et al., 2013). As for adhesins, aggregation substances are considered virulence factors. However, the safety assessment of strains harboring adhesins or aggregation substances may highly depend on the localization of such genes on mobile genetic elements and on other safety aspects of the strain. However, the difference in infectivity between weissellas that are either probiotic or involved in infections such as endocarditis, cannot be explained by differences in adherence potential alone, but other factors involved in promoting disease must exist in pathogenic strains, as was similarly postulated by Vankerckhoven et al. (2007) for lactobacilli involved in human infections.

Genes for mucus-binding protein (Mub), which can serve as effector molecules involved in mechanisms of adherence of bacteria to the host, were detected in W. ceti NC36 and W. confusa LBAE C39-2 (Table 2) genome sequences. The phylogenetic tree of nucleotide sequences encoding mucus-binding proteins of weissellas, as well as of the closely related genera Leuconostoc, Lactobacillus, and Enterococcus, showed that the W. ceti NC36 mub gene clustered closely with Enterococcus sp. C1 mub in the same group together with sequences from Lb. delbrueckii and Leuconostoc. However, the mub of W. confusa LBAE C39-2 clustered with that of Lb. plantarum (Figure 3). The presence of mucus-binding protein may be a desirable feature in probiotic bacteria, as it may play an important role in the adhesion of the probiotic strain to host surfaces (Mack et al., 1999). However, this property is obviously problematic in potentially pathogenic strains.

Regarding other virulence factors, such as the Serine-rich adhesin for platelets, which is also important in bacterial adhesion and is considered the central event in the pathogenesis of infective endocarditis (Sullam, 1994), this adhesin was only detected in the pathogen W. ceti NC36 (WCNC_RS02030; Table 2). On the other hand, the gene encoding the Serine-rich adhesin for platelets was detected also in probiotic lactobacilli such as Lb. johnsonii NCC533 and Lb. reuteri (Zhou and Wu, 2009), but not in leuconostocs. Concerning the staphylococcal surface protein A, which is involved in invasion and infectivity, several genes coding for a similar protein were detected in W. ceti WS08 (WS08_0360, WS08_0450, WS08_0978, WS08_1156, WS08_1190), W. ceti WS74 (WS74_0360, WS74_0451, WS74_1225, WS74_1261), and W. ceti WS105 (WS105_0358, WS105_0448, WS105_1219, WS105_1255). However, no homologous genes were detected in either leuconostocs or in lactobacilli (Table 2). Due to the low homology of virulence determinants in weissellas, it is difficult to detect such genes by PCR, thus genome sequencing would be the only way to detect and identify these determinants.

The presence of genes for hemolysin or hemolysin-like proteins in weissellas was revealed by in silico analysis of the annotated genomes sequences (Table 2). The ubiquitous occurrence of such genes in probiotic lactobacilli and bifidobacteria, and also in other LAB such as leuconostocs, may raise questions about their function and virulence potential. The role of these genes in LAB virulence is unknown, and their presence in the genome of a strain intended to be used as probiotic should not necessarily be an exclusion factor for targeting strains for probiotic use. As shown in Table 2, weissellas harbored in their genome 1–3 hemolysin encoding genes, i.e., genes for hemolysin A and also hemolysin-like proteins.

**Antibiotic Resistance**

Studies on antibiotic resistance profiles in Weissella genus are very limited, and MIC breakpoints have not been defined by EFSA. Thus, to categorize weissellas as sensitive or resistant to different antibiotics of clinical relevance is a difficult task. These bacteria are known for their intrinsic resistance to antibiotics inhibiting cell wall biosynthesis such as vancomycin and fosfomycin, similar to other Gram-positive bacteria (Arca et al., 1997), and also to antibiotics that inhibit tetrahydrofolate biosynthesis such as sulfamethoxazol and trimethoprim (Liu et al., 2009). Furthermore, resistance to gentamicin, kanamycin, and norfloxacin was also reported in food-associated weissellas (Patel et al., 2012).

Reports about molecular detection of antibiotic resistance genes in weissellas are very scarce, possibly due to the high divergence of resistance genes. In this sense, only mef(A/E)
drug efflux pump genes involved in the active efflux of macrolides (Clancy et al., 1996; Tait-Kamradt et al., 1997) were detected in W. cibaria of aquatic origin (Muñoz-Atienza et al., 2013). When we analyzed the in silico genome sequences of Weissella spp., different antibiotic resistance genes were detected, such as those coding for fosfomycin and methicillin resistance proteins in almost all the genomes of Weissella strains sequenced (Table 3) to date. For example, the fosB gene coding for fosfomycin resistance was detected in W. ceti WS08 (WS08_1256), W. ceti WS74 (WS74_1327) and W. ceti WS105 (WS105_1321), and nucleotide sequences of the genes were identical in all cases. In addition, other weissellas harbored multidrug transporters involved in fosfomycin resistance and deoxycholate resistance, as was the case for W. ceti NC36 (WCNC_RS02205), W. cibaria KACC 11862 (ESE_RS0109255, ESE_RS0102540, ESE_RS0105180), W. ceti NC36 (WCNC_RS02205), and W. cibaria KACC 11862 (ESE_RS0109255, ESE_RS0102540, ESE_RS0105180). However, the use of multidrug transporters is rare among Weissella species, especially when infection treatment with a combination of other antibiotics is possible.

### Table 3: Antibiotic resistance genes of Weissella species as revealed by in silico screening of the annotated genome sequences.

| Strains          | Antibiotic resistance determinants detected by analysis in silico of genome sequences (locus_tag) |
|------------------|-------------------------------------------------------------------------------------------------|
|                  | Daunorubicin | Fosfomycin | Methicillin | Glycopeptide | Sulfonamide | Tetracycline |
| W. ceti WS08     | –           | 1 FosB (WS08_1256) | –           | –           | Sul (WS08_0966) | –           |
| W. ceti WS74     | –           | 1 FosB (WS74_1327) | –           | –           | Sul (WS74_1032) | –           |
| W. ceti WS105    | –           | 1 FosB (WS105_1321) | –           | –           | Sul (WS105_1028) | Tet (WS105_0392) |
| W. ceti NC36     | –           | 1 MDT-FosB (WCNC_RS02205) | 2 MRP (WCNC_RS2142, WCNC_RS02627) | –           | –           | –           |
| W. cibaria KACC 11862 | –           | 1 MDT-FosB (ESE_RS0106205) | 3 MRP (ESE_RS0109255, ESE_RS0102540, ESE_RS0105180) | –           | –           | –           |
| W. confusa LBAE C39-2 | –           | 1 MDT-FosB (WEISSC39_RS01350) | 1 MRP (WEISSC39_RS07670) | –           | VanZ (ESE_RS0111030) | –           |
| W. halotolerans  | 1 DrrC (G414_RS010140) | 1 MDT-FosB (G414_RS010540) | 2 MRP (G414_RS0103120) | –           | –           | –           |
| DSM 20190        | 1 DrrC (TC24_RS09650) | 1 MDT-FosB (TC24_RS09650) | 2 MRP (TC24_RS07475, TC24_RS0485) | –           | –           | –           |
| W. hellenica     | –           | –           | 2 MRP (WC22_RS01735, WC22_RS02350) | –           | –           | –           |
| Wikim14          | –           | –           | 2 MRP (WC22_RS02350) | –           | –           | –           |
| W. koreensis     | –           | 1 MDT-FosB (JC2156_RS02465) | 2 MRP (JC2156_RS06850, JC2156_0740) | –           | –           | –           |
| KACC 15510       | –           | –           | 2 MRP (JC2156_RS06850, JC2156_0740) | –           | –           | –           |
| W. koreensis     | –           | 1 MDT-FosB (WOSG25_RS02065) | 2 MRP (WOSG25_RS01020, WOSG25_RS07655) | –           | –           | –           |
| KCTC 3621        | –           | –           | 2 MRP (WOSG25_RS01020, WOSG25_RS07655) | –           | –           | –           |
| W. oryzae SG25   | 1 DrrC (WOSG25_RS07165) | 1 MDT-FosB (WOSG25_RS02065) | 2 MRP (WOSG25_RS01020, WOSG25_RS07655) | –           | –           | –           |
| W. paramesenteroides ATCC 33313 | –           | 1 MDT-FosB (HMPREF0877_RS05895) | 2 MRP (HMPREF0877_RS03440, HMPREF0877_RS07670) | VanZ (HMPREF0877_1234) | –           | –           |
| W. thailandensis | –           | –           | 1 MRP (WT2_00144) | –           | –           | Tet (WT2_00189) |
| fsh4-2           | –           | –           | –           | –           | –           | –           |
| Weissella sp.    | ND          | ND          | ND          | ND          | ND          | sul1, sul2 genes* |

DrrC, daunorubicin resistance protein; FosB, fosfomycin resistance protein; MDT-FosB, multidrug transporter involved in fosfomycin resistance; MRP, methicillin resistance protein; Sul, sulfonamide resistance protein; Tet, tetracycline resistance protein; VanZ, glycopeptide resistance protein. *Byrne-Bailey et al. (2009).

Figure 4: Weissella species showing clusters to cluster into two groups. High similarities in sequences again suggested an evolutionary relationship of weissellas, leuconostocs, enterococci, and lactobacilli (Figure 4) sequences. Fosfomycin is a broad antibacterial agent that targets several pathogens such as Haemophilus spp., Staphylococcus spp. and most of the enteric gram-negative bacteria. Although no cross resistances are known to occur for other antibiotics, there are no data on whether or not the fosB gene is transferable to other bacteria. Thus, weissellas harboring the fosB gene should be investigated in terms of the transferability of this gene, especially to pathogens. In the case of enterococci, these bacteria contain a conjugative plasmid that harbors the novel fosB transposon (ISL3-like transposon), as well as the Tn1546-like transposon (containing vanA and fosB, Qu et al. (2014)). Should weissellas harbor no transferable fosB gene, a potential prophylactic use of these bacteria should be possible, especially when infection treatment with a combination of other antibiotics is possible.

The intrinsic resistance of weissellas toward vancomycin may be attributed to the absence of D-Ala-D-lactate in their cell wall, which is the target of vancomycin. A similar situation exists in other LAB such as Lactobacillus, Pediococcus, and Leuconostoc species. Thus, such resistance cannot be attributed to acquisition of resistance genes. Nevertheless, some...
Weissellas harbored in their genomes the $vanZ$ resistance gene, as is the case for *W. cibaria* KACC 11862 (ESE_RS0111030), *W. confusa* LBAE C39-2 (WEISSC39_RS04975), and *W. paramesenteroides* ATCC 33313 (HMPREF0877_1234). This gene confers resistance to teicoplanin and does not involve the incorporation of a substituent of D-alanine into the peptidoglycan precursors (Arthur et al., 1995; Table 3).

No data have been reported on methicillin resistance to date. However, analyzing the *in silico* genome sequences of weissellas available in NCBI database, methicillin resistance protein encoding genes were detected in all weissellas (sequenced genomes of nine species; Table 3). Methicillin resistance proteins are found in *Staphylococcus* spp. and especially in *S. aureus*, and the presence of genes encoding such proteins in *Weissella* species may suggest a horizontal gene transfer between the genera. The alignment of nucleotide sequences for methicillin resistance protein in weissellas and other Gram-positive bacteria (*S. aureus, Leuconostoc, E. faecalis*, and *Lactococcus*) clearly showed an evolutionary relationship between the methicillin-resistance sequences of *Weissella* and the other Gram-positive bacteria *S. aureus, Leuconostoc, and E. faecalis* (Figure 5). The dendrogram showed two main groups, in which the genes from *Weissella* spp. were distributed regardless of the species, strain or origin. A divergence of methicillin resistance genes could even be observed in a single strain of *W. ceti* NC36, which carried multiple methicillin resistance genes, varying considerably in nucleotide sequence (Figure 5). On the other hand, one of two genes encoding for methicillin resistance in *W. cibaria* KACC 11862 (ESE_RS0105180) formed a single lineage, as such being divergent from the other weissellas and other Gram-positive bacteria (Figure 5). Further studies should elucidate the functionality of the methicillin resistance genes of weissellas, and the transferability of these genes to other bacteria.

Sulfonamide resistance could be due either to mutation in the chromosomal gene that mediates dihydropteroate synthesis, which is a folic acid precursor, or to the acquisition of resistance genes coding for resistant forms of the enzyme (Franklin and Snow, 2005). Resistance of weissellas to sulfonamides was reported by Byrne-Bailey et al. (2009) in *Weissella* spp. isolated from un-amended pig slurry and relied on the presence of sul1 and sul2 resistance genes. Figueiredo et al. (2012) isolated sulfonamide-resistant *W. ceti* that caused outbreaks characterized by acute haemorrhagic septicaemia and high mortality rates in rainbow trout. However, no genetic elements responsible for this resistance were described. *Weissella* genomes investigated in this study showed the presence of sulfonamide-resistance genes in *W. ceti* strains WS08 (WS08_0966), WS74 (WS74_1032), and WS105 (WS105_1028) isolated from rainbow trout (Figueiredo et al., 2012). Overall, resistance to vancomycin, fosfomycin, and sulfonamides appears to be a common trait in the genera *Weissella* and *Leuconostoc*. On the other hand, it is frequent that bacterial resistance to sulfonamides often co-exists with trimethoprim resistance, since this substance is used in combination with sulfonamides to minimize bacterial resistance. The known *dfr* trimethoprim resistance genes, which are usually associated with integrons (Skold, 2001) could, however, not be detected in any of the *Weissella* genome sequences analyzed here. Thus, the reported resistance of *W. confusa* (Fairfax et al., 2014; Medford et al., 2014) to trimethoprim may be caused by other modifications than those produced in the target enzyme dihydrofolate reductase (Dfr) that is encoded by the *dfr*-genes.

*Weissella* are generally susceptible toward tetracycline. Screening of the published genomes revealed the presence of a gene encoding tetracycline (class C) resistance in *W. ceti* WS105 (WS105_0392) and in *W. thailandensis* fsh4-2 (WT2_00189; Table 3).

It is frequent to find resistance to the most widely used chemotherapeutic agent daunorubicin in probiotic bacteria such as lactobacilli (*Lb. acidophilus* NCFM, *Lb. casei* BD11) and bifidobacteria (*Bifidobacterium animalis* subsp. *lactis* Bb-12, *Bifidobacterium longum* subsp. *infantis* ATCC 15697). When the annotated genome sequences of weissellas were
screened for daunorubicin resistance genes, ABC transporter-based resistance genes could be found in several Weissella spp. \([W.\ halotolerans\ DSM\ 20190\ (G414\_RS0101040),\ W.\ hellenica\ Wikim14\ (TY24\_RS06500),\ and\ W.\ oryzae\ SG25\ (WOSG25\_RS07165)]\) (Table 3).

Antibiotic resistance is often based on unspecific mechanisms such as efflux pumps, which are widespread throughout evolution in different bacteria and can pump a variety of drugs out the cells (Piddock, 2006). When we screened the annotated genome sequences of Weissella spp., several efflux pumps were detected, such as multiple antibiotic resistance protein MarR, multidrug resistance SMR family protein, MFS multidrug transporter, ABC transporter, and a DedA family protein, which was recently shown to be associated with antibiotic resistance (Kumar and Doerrler, 2014).

### Species-Specific Comparison of Biotechnological and Biosafety Issues

Based on our genomic in silico investigation, the potential deleterious and beneficial effects for each of the Weissella species in view of their application as starter cultures or probiotics are discussed below, highlighting the controversial issue of strains of the same species being industrially important in some cases, while being problematic from a safety point of view in others.

#### Weissella ceti

Weissella ceti (Vela et al., 2011) was isolated from different organs of beaked whales (Mesoplodon bidens) such as the spleen, kidney, muscle, brain, and lymph. Several strains of W. ceti were reported as pathogens in fish, such as W. ceti WS08, W. ceti WS74, and W. ceti WS105 from farmed rainbow trout in Brazil (Figueiredo et al., 2014; Costa et al., 2015), and W. ceti NC36 from farmed rainbow trout in the United States (Ladner et al., 2013). This suggests that weissellosis is a rapidly emerging disease in farmed rainbow trout in different geographical locations. Recently, Welch and Good (2013) reported that Weissella spp. closely related with W. ceti strains on the basis of their 16S rRNA gene sequences (99% identity) from Chinese and Brazilian outbreaks were involved in mortality of farmed rainbow trout in the USA. On the other hand, no reports were found on the application of W. ceti strains as starter cultures or as probiotics. In this study it was found that W. ceti genomes harbored several virulence factors and antibiotic resistance genes, which point toward a pathogenic potential. The industrial application of such strains thus seems problematic and should be considered carefully on a strain to strain basis in the background of a detailed safety evaluation for the presence of antibiotic resistances and virulence determinants.

#### Weissella cibaria

Originally isolated from Thai fermented foods (Björkroth et al., 2002), W. cibaria was also isolated from other sources such as...
as sourdough, fermented milk, cheese, fermented vegetables, fermented fish and meat, and also silage (Srionnual et al., 2007; reviewed by Fusco et al., 2015). However, clinical samples have also been a source of *W. cibaria* (Björkroth et al., 2002), with these bacteria being found in human saliva and the vagina, in human and animal feces and milk, and also in human blood and urine (reviewed by Fusco et al., 2015).

*Weissella cibaria* has been targeted for use as starter culture in foods for different purposes such as for probiotic effects. In this sense, the dextran produced by dextranucrase from *W. cibaria* JAG8 had potential prebiotic effect for health benefits, stimulating the growth of probiotic bacteria (Tingirikari et al., 2014). Other beneficial effect of *W. cibaria* were suggested to be its capacity to produce higher levels of exopolysaccharides (EPS), which indicates more acid resistance, thus improving its probiotic capacity during passage throughout gastrointestinal tract (Park et al., 2013). Potentially probiotic *W. cibaria* strains were isolated from kimchi and also from goat milk (Elavarasi et al., 2014), and some strains were suggested to have anticancer activity, immune modulating activity, anti-inflammatory activity, antioxidant activity (patent related to the *W. cibaria*’s antioxidant activity registered by Cha et al., 2008; Kang et al., 2011; Kwak et al., 2014), antiviral activity (the avian influenza virus; Rhö et al., 2009) and anti-obesity effects being suggested to be more effective than the well-known probiotic bacteria *Lb. rhamnosus* GG (LGG; Ahn et al., 2013). It was also reported that the water-soluble polymers produced by *W. cibaria* inhibited biofilm formation by *Streptococcus mutans*, and thus production of such compounds could reduce oral plaque formation by approximately 20.7% *in vivo* and *in vitro* (Kang et al., 2006). Furthermore, the same authors reported that the hydrogen peroxide produced by *W. cibaria* inhibited the growth of the bacterial agent of periodontal disease, *Fusobacterium nucleatum*, and was effective in reducing the production of hydrogen sulfide and methanethiol responsible for the associated foul smell (Kang et al., 2006).

Several reports proposed different strains of *W. cibaria* as starter cultures in different fermentations, and these were based on its antimicrobial capacity. *W. cibaria* strains produce a variety of antagonistic substances, including organic acids and bacteriocins (i.e., weissellicin 110 produced by *W. cibaria* 110; Srionnual et al., 2007), as mentioned above. Wolter et al. (2014) reported that exopolysaccharide-producing *W. cibaria* MG1 might be a suitable starter culture for sourdough fermentation of buckwheat, quinoa and teff flour. *W. cibaria* was successfully tested in a defined semi-liquid sourdough starter (Gaggiano et al., 2007; Ricciardi et al., 2009), and due to its ability to grow at 45°C and produce EPS, which could be used as an alternative to additives for conditioning the textural properties of bread (Di Cagno et al., 2006), it was considered to be a suitable strain for this application. *Weissella cibaria* could also play an important role in meat fermentation. Thongsanit et al. (2009) proposed *W. cibaria* MSS2 as starter culture for the production of *nham* fermented sausage and for kimchi, due to the capacity of these bacteria to produce glutaminase, which is indispensable in food processing. Furthermore, the use of *W. cibaria* as starter for food fermentations promoted the formation of ornithine from arginine, which in turn may have beneficial health effects, such as anti-obesity effect due to high levels of ornithine in fermented foods (Yu et al., 2009).

On the other hand, *W. cibaria* was reported as an emerging pathogen being associated with bacteremia (Kulwichit et al., 2008) and dog ear otitis (Björkroth et al., 2002), and also as food spoilage organism in sliced vacuum-packed cooked ham (Han et al., 2010). In the present study, we showed that *W. cibaria* KACC 11862 harbored in its genome some virulence determinants (hemolysins) and antibiotic resistance genes (fosfomycin, methicillin, and glycopeptide; Tables 2–3). This argues for a detailed investigation on the virulence potential for this species on a strain basis.

### Weissella confusa

Due to its previous confusion with viridans streptococci, most of infections caused by *W. confusa* were underestimated due to the misidentification of this bacterium by commercial identification systems. When the genus *Weissella* was described by Collins et al. (1993), it was shown that *W. confusa* played an important role in human and animal sepsis and also bacteremia (Green et al., 1990; Olano et al., 2001; Björkroth et al., 2002; Plaherty et al., 2007; Shin et al., 2007; Salimnia et al., 2010, 2011; Harlan et al., 2011; Kumar et al., 2011; Lee et al., 2011; Fairfax and Salimnia, 2012), thumb abscess (Bantar et al., 1991), endocarditis (Shin et al., 2007), osteomyelitis (Kulwichit et al., 2007), and recently it was also shown to be involved in infection of a prosthetic joint (Medford et al., 2014). Here, in silico analysis of the *W. confusa* LBAE C39-2 genome showed the presence of virulence determinant genes (encoding collagen adhesion, hemolysin, and mucus-binding proteins) and antibiotic resistance genes (fosfomycin, methicillin, and glycopeptide; Tables 2–3).

On the other hand, due to the widespread use of *W. confusa* in fermented foods (sourdough, cereals, vegetables, fermented milk, cheese; reviewed by Fusco et al., 2015), it was proposed as a starter culture, and also as probiotic which provides various beneficial health effects such as the inhibition of *Helicobacter pylori*, a bacterium that causes chronic inflammation and ulcers in the stomach (Nam et al., 2002). Furthermore, *W. confusa* strains isolated from human feces were proposed as potential probiotics (Lee et al., 2012). Other *W. confusa* strains (UI006 and UI007) isolated from traditional dairy foods from Nigeria were proposed as adjunct cultures for the dairy manufacture industry, because of their antagonistic activities against entero- and uro-pathogens (organic acids, ethanol, and hydrogen peroxide), and their lack of toxic compounds (Ayeni et al., 2009, 2011). In this regard Yang (2013) proposed *W. confusa* LK4 isolated from leek kimchi as a functional starter culture for fermentation of leeks. Due to the aforementioned role in human infections, the biotechnological use of *W. confusa* should also be carefully assessed on a strain to strain basis.

### Weissella koreensis

These bacteria isolated from a Korean fermented food "kimchi" (Lee et al., 2002) was used as starter culture in kimchi
fermentations and production of functional foods, since *W. koreensis* OKI-6 has anti-obesity effects in high-fat diet (HF) induced obese mice (Park et al., 2012). Moon et al. (2012) reported the same anti-obesity effect for *W. koreensis* OKI-6, which produced ornithine from arginine, implying its functional role in reducing obesity. Also, Pi et al. (2014) showed that *W. koreensis* 521 was able to prevent and suppress obesity via the inhibition of pre-adipocyte mitogenesis and differentiation. On the other hand, the application of *W. koreensis* as starter culture together with *Lactobacillus citreum* and baker’s yeast in sourdough to make whole wheat bread was also considered as successful, since a good texture and an extended shelf-life of bread could be obtained (Choi et al., 2012). The use of *W. koreensis* as starter culture in broken rice was also found to provide good organoleptic properties to *jeungpyeong*, which is a Korean fermented rice cake (Choi et al., 2013). *Weissella koreensis* was also proposed for use as probiotic in pigs, since dietary supplementation with *W. koreensis* WKG2 in growing pigs could improve the average daily gain (ADG) and could have a beneficial effect on the immune response during an inflammatory challenge (Wang et al., 2014). On the other hand, no negative effects on heath were yet attributed to this species. However, in our *in silico* genome investigation, we showed the presence of potential virulence determinants and antibiotic resistance genes in some strains of *W. koreensis* (Tables 2–3), again indicating that a safety assessment for strains targeted for biotechnological use should be done.

**Other Weissella spp.**

Regarding their health-promoting activities, several species of *Weissella* exhibited beneficial effects. *W. kimchii* is a hydrogen peroxide-producing species that has been proposed as probiotic to prevent vaginal infections against *Candida albicans*, *Escherichia coli*, *S. aureus*, and *Streptococcus agalactiae* (Lee, 2005; Lee et al., 2011). *W. hellenica* was isolated from different sources such as fermented vegetables, fermented sausage, fermented fish, cheeses, cow’s milk and flounder intestine (Leong et al., 2013; reviewed by Fusco et al., 2015), and is known for its potential probiotic activity due to its bacteriocin-producing capacity (weissellicins D, L, M, and Y). Strains from this species are active against several pathogens (Masuda et al., 2011; Leong et al., 2013; Chen et al., 2014) and have potential also as bio-protective culture to improve safety and shelf-life of foods like tofu (Chen et al., 2014). *W. hellenica* strains isolated from different sources (cheese, fermented sausage, fermented vegetables, cow’s milk, flounder intestine; reviewed by Fusco et al., 2015) were also reported as glucan (EPS) producers (Kim et al., 2008), which may have industrial applications. Finally, *W. paramesenteroides* isolated from soil, vegetables, cheese, fermented sausage, fermented sea food, fermented vegetables and also from feces, cow’s milk, and gut of rainbow (reviewed by Fusco et al., 2015) can have antibacterial activity by production of bacteriocins such as weissellin A from *W. paramesenteroides* DX (Papagianni and Papamichail, 2011), a bacteriocin from *W. paramesenteroides* DFR-8 (Pal and Ramana, 2010), and also non-proteinaceous antibacterial compounds (Pal and Ramana, 2009) with a broad inhibitory spectrum against Gram-positive and Gram-negative bacteria. These strains may therefore be interesting for their use as food biopreservatives. On the detrimental side, Han et al. (2010) showed that *W. paramesenteroides* was involved in sliced vacuum-packed cooked ham spoilage.

Due to their heterofermentative metabolism, some weissellas are also involved in food spoilage and lead to sensory defects of, e.g., meat products (Marsden et al., 2009). In this regards, *W. viridescens* plays an important role in meat spoilage, producing a greenish slime on meat surfaces as a result of its production of H₂O₂. In cooked hams, formation of cavities can result from the production of CO₂ by these bacteria. Furthermore, taking into account data presented here from *in silico* analyses of *Weissella* spp. genomes, the presence of virulence determinants, especially hemolysins, were detected in all strains analyzed. Also antibiotic resistance genes, such as those coding for fosfomycin and methicillin resistances (Tables 2–3), occur in this species. Also in this case, therefore, the safety of strains intended for industrial use should be investigated for each strain in detail.

**CONCLUSION**

Considering the large number of health-promoting benefits which could arise from the use of strains of *Weissella* spp., such as antibacterial, anti-viral, anti-tumoral, anti-obesity, anti-inflammatory, and antioxidant activities, several weissellas could be targeted for use as starter cultures or probiotics. By contrast, specific strains of *Weissella* species have also been involved as pathogens in the etiology of different diseases such as bacteremia, endocarditis, sepsis, and may even cause mortality. In fact, the safety of this genus has not been deeply studied, as only some strains are considered as opportunistic pathogens. Thus, the application of strains in foods and feeds or for humans as probiotics should be done with caution. In this report we showed that screening of genome sequences revealed the presence of several virulence and antibiotic resistance genes, which could be the basis of the potential pathogenicity of some strains. However, the presence of single determinants should not be an exclusion criterium for weissellas that may have overall beneficial effects. Thus, selection of weissellas intended to be used as starters or as probiotics should be investigated carefully regarding their safety aspects, preferably by genome sequencing an annotation, since the heterogeneity in nucleotide sequences of well-known virulence and antibiotic resistance-genes make these undetectable by PCR methods. Generally, the application of *W. confusa* and *W. cibaria* strains as starter cultures or as probiotics should be approached with caution, carefully selecting strains which lack pathogenic potential and which do not possess transferable antibiotic resistance genes.

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