



# Advances in the genomics and metabolomics of dairy lactobacilli: A review



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## ABSTRACT

The *Lactobacillus* genus represents the largest and most diverse genera of all the lactic acid bacteria (LAB), encompassing species with applications in industrial, biotechnological and medical fields. The increasing number of available *Lactobacillus* genome sequences has allowed understanding of genetic and metabolic potential of this LAB group. Pangenome and core genome studies are available for numerous species, demonstrating the plasticity of the *Lactobacillus* genomes and providing the evidence of niche adaptability. Advancements in the application of lactobacilli in the dairy industry lie in exploring the genetic background of their commercially important characteristics, such as flavour development potential or resistance to the phage attack. The integration of available genomic and metabolomic data through the generation of genome scale metabolic models has enabled the development of computational models that predict the behaviour of organisms under specific conditions and present a route to metabolic engineering. Lactobacilli are recognised as potential cell factories, confirmed by the successful production of many compounds. In this review, we discuss the current knowledge of genomics, metabolomics and metabolic engineering of the prevalent *Lactobacillus* species associated with the production of fermented dairy foods. In-depth understanding of their characteristics opens the possibilities for their future knowledge-based applications.

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## 1. Introduction

The lactic acid bacteria (LAB) are a group of Gram-positive, non-sporulating, aerotolerant bacteria, with a fermentative metabolism that has lactic acid as the principal final product. The LAB group comprises seven genera: *Lactococcus*, *Lactobacillus*, *Enterococcus*, *Pediococcus*, *Streptococcus*, *Leuconostoc* and *Oenococcus* (O'Sullivan et al., 2009). The practical importance of the organisms within this group is unquestionable as they find application in industry, food and health-related fields. In the food industry, LAB are widely used in the production of fermented dairy, meat and vegetable products as well as in wine and sourdough production (Pfeiler and Klaenhammer, 2007; O'Sullivan et al., 2009). In addition, the production of antimicrobials or bacteriocins by certain species of the LAB has prompted their use as biopreservative agents in foods (Cleveland et al., 2001; Cotter et al., 2005; De Vuyst and Leroy, 2007). Other members of the LAB group exhibit health benefits and are often used as probiotics in the treatment of intestinal infections, inflammatory bowel disease and allergy development (Ljungh and Wadstrom, 2006). Members of the LAB group have also been suggested for use in mucosal vaccines as delivery vehicles for vaccine antigens (Bermudez-Humaran et al., 2011; Villena et al., 2011; Wyszynska et al., 2015). The wide variety and number of applications of the LAB raises the need to correlate industrially and clinically important features with genomic information to examine the possibilities for exploitation of their metabolic potential, thus improving their use in biotechnological and health-related applications. The complete and draft genomes of many LAB species are available in online databases (Genome Online Database, <https://gold.jgi.doe.gov/>), NCBI database <http://www.ncbi.nlm.nih.gov/genome/>, Ensemble Genomes database <http://ensemblgenomes.org/>, etc.) and they present valuable sources of information regarding genetic diversity and the metabolic potential of strains. In addition, state-of-the-art developments in genomics and metabolomics provide the tools for a more 'knowledge-based' approach to selection of desirable cultures for application in industry (McAuliffe, in press).

LAB are phylogenetically closely related, but the number of predicted protein-coding genes in the LAB varies between 1700 and 2800 (Makarova et al., 2006). Genomic studies of members of the LAB have confirmed the overall trend of minimisation of genomes, which is in close agreement with the transition to nutritionally rich environments. Nevertheless, some gene families were expanded by gene duplication or acquisition of paralogous genes via horizontal gene transfer (HGT) (Makarova et al., 2006). Based on the analysis of the genomes of 12 LAB species it was concluded that the core LAB genome, comprising orthologous genes conserved in all analysed genomes (Collins and Higgs, 2012), consists of 567 genes, mostly encoding translation, transcription and replication processes, but 41 of the genes were uncharacterized and 50 had only general functions predicted. This study also identified two core genes exclusive for LAB, the products of which are LysM (peptidoglycan-binding) domain and the highly conserved LaCOG01237 with no known domains, but based on its localisation, it is probably involved in modification of tRNA (Makarova et al., 2006).

The genus *Lactobacillus* comprises a diverse group of bacteria currently consisting of more than 200 species and subspecies (Sun

et al., 2015a) that share the common features of other LAB, including low GC content, acid tolerance and conversion of sugars to lactic acid as one of the main end products of metabolism. Species of lactobacilli are present in various environments such as plants, fermented food products (dairy, meat, wine), and both the human and animal gastrointestinal tracts. Their ability to ferment milk, meat and plant material presents the basis for their artisanal and industrial usage (Sun et al., 2015a). Apart from this, strains of *Lactobacillus* are well known for their probiotic properties (Lebeer et al., 2008).

This review aims to present recent findings related to the genus *Lactobacillus*, with a particular emphasis on strains commonly used in the production of fermented dairy foods. Genomic features of the main dairy species will be discussed, including their remarkable niche specialisation. Advancements in our knowledge through genomic analysis of key attributes of dairy species will also be reviewed. Finally, innovations in the applications of genome scale metabolic models and metabolic engineering, highlighting new possibilities in exploitation of strains of *Lactobacillus*, are also discussed.

## 2. Genomics of the *Lactobacillus* genus

Due to their importance in various biotechnological and health-related applications, there has been a growing interest in exploring the genomic features of the genus *Lactobacillus*, which is the largest and most diverse genus of LAB (Broadbent et al., 2012). *Lactobacillus* genomes range in size from 1.23 Mbp (*Lb. sanfranciscensis*) to 4.91 Mbp (*Lb. parakefiri*) (Sun et al., 2015a). Species of this genus are present in dairy products (*Lb. delbrueckii* ssp. *bulgaricus*, *Lb. helveticus*), human and animal gastrointestinal tracts (*Lb. acidophilus* and *Lb. gasseri*) or in a variety of niches (*Lb. plantarum*, *Lb. pentosus*, *Lb. brevis*, and *Lb. paracasei*) (Smokvina et al., 2013). The first genome of the *Lactobacillus* genus sequenced was *Lb. plantarum* WCFS1 (Kleerebezem et al., 2003) followed by *Lb. johnsonii* NC533 (Pridmore et al., 2004) and *Lb. acidophilus* NCFM (Altermann et al., 2005). These studies revealed some interesting genomic features of the *Lactobacillus* genus, such as lifestyle adaptation islands in *Lb. plantarum* WCFS1, lack of general biosynthetic pathways in the probiotic strain *Lb. johnsonii* NC553 and unique structures called potential autonomous units (PAU) in *Lb. acidophilus* NCFM, all of which triggered further investigation and comparison with newly sequenced strains of the same species. Currently (July 2016), there are 214 *Lactobacillus* genome sequencing projects available in public databases (<http://www.ncbi.nlm.nih.gov>).

The pangenome (or supragenome) is considered as the full set of all genes within a selected genome set (species, genera or higher taxonomic groups) (Medini et al., 2005; Collins and Higgs, 2012). The size of the pangenome generated for *Lactobacillus* and associated genera of LAB reaches almost 45,000 gene families, while 73 genes mainly responsible for cell growth and replication make up the core genome (Sun et al., 2015a). In a study based on the features of 20 complete *Lactobacillus* genomes representing 14 species whose genomes ranged from 1.8 to 3.3 Mbp, the number of proteins within these genomes was between 1721 and 3100 (Kant et al., 2011). The estimated size of the pangenome of the *Lactobacillus* genus consists of almost 14,000 proteins, while the core genome

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