



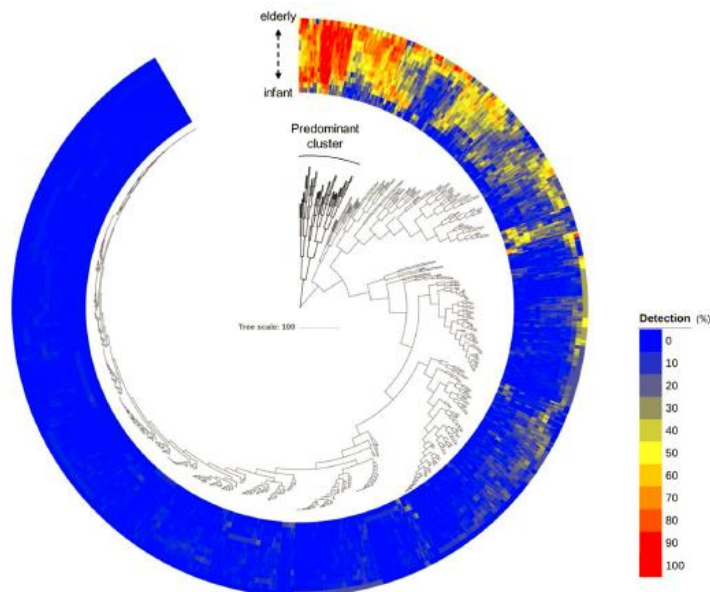
## New Genome Study of *B. longum* subsp. *longum* by Morinaga Milk May Explain the Species' Wide Distribution Across All Ages

**TOKYO (FEBRUARY 14, 2018)** — *Bifidobacterium longum* is one of only a handful of species of gut bacteria that is widely present among people of all ages, including infants, adults and the elderly.<sup>1,2</sup> Today, [Morinaga Milk Industry Co., Ltd.](#), a leading Japanese dairy product company, announced the results of a groundbreaking new genome study, in collaboration with the SFI Research Centre *APC Microbiome Ireland*, that may explain why.

The human gut is colonized by a collection of microbes (microbiome) which play an integral role in human health, by helping us digest our food, produce certain vitamins, regulate our immune system, and protect us against pathogenic bacteria. This current study revealed that one bacterial species, *B. longum* subsp. *longum*, demonstrates a wide variation in its genes that increases its competitiveness in the gut environment, because its genome adapts to the changing diet of each generation. In addition, it suggests that *B. longum* subsp. *longum* is extensively transmitted between relatives, and that such transmission does not occur only between mothers and infants, as previously believed, but also between other family members and even across three generations.<sup>3</sup>

### Study Overview

For the study, a total of 453 fecal samples were collected from healthy Japanese subjects aged 0 to 104 years, as a means of measuring the bacterial species present in the gut. In total, 871 different bacterial species were detected (Fig.1), but only three species (*Blautia wexlerae*, *Streptococcus salivarius* and *Bifidobacterium longum*) were found to be present in more than 50% of the subjects across all generations.



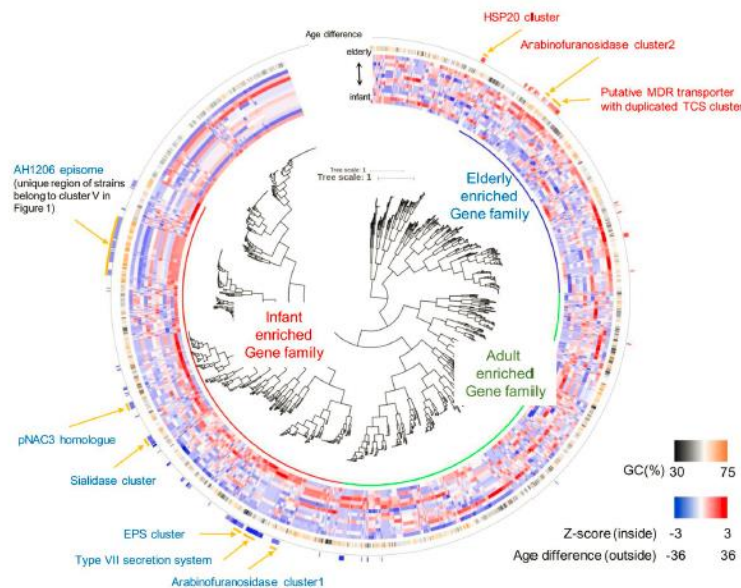
(Fig.1) Distribution of gut microbiota in healthy Japanese subjects

This finding highlights the broad distribution of *B. longum* across the human lifespan. In order to identify the mechanism that allows a specific species to be so ubiquitous, Morinaga, in collaboration with the SFI Research Centre *APC Microbiome Ireland* at the National University of Ireland, Cork, performed a comparative genome analysis on various strains of *B. longum* subsp. *longum* to determine genetic differences among strains isolated from people of varying ages.

### ***B. longum* subsp. *longum* Strains Separated into Seven Clusters**

Comparative analyses involving 145 *B. longum* representatives obtained from Japanese subjects, including 32 publicly available genomes, showed that *B. longum* subsp. *longum* strains can be grouped into seven clusters depending on the presence of prophage (i.e. viral material) and/or a megaplasmid (i.e. genetic material being present outside of the bacterial chromosome).

No correlation was observed between isolated strains and subject age, although a significant negative correlation was found between the number of identified genes present in the strains and subject age. This suggests that *B. longum* subsp. *longum* strains isolated from younger subjects possess, on average, a higher number of genes compared to the ones from older subjects. Researchers performed further investigation to identify genes in each strain isolated from different age groups, and as a result, gene families were classified into four groups: infant, adult, elderly-predominant gene families, and genes that exhibit no relationship with subjects age (Fig.2).



(Fig.2) Genes enriched in *B. longum* subsp. *longum* strains isolated from subjects of varying age

### ***Infant-associated Strains More Adapted to Utilize Carbohydrates Found in Human Milk***

Researchers frequently found strains in *B. longum* subsp. *longum* from younger subjects, which possess genetic code that is related to sugar utilization, including that of the sugar sialic acid which is one of the components of Human Milk Oligosaccharides (HMOs) that are found in breast milk. This characteristic may be an adaptive strategy of *B. longum* to survive the infant gut environment by utilizing components from the mother's breast milk.

### ***Elderly-associated Strains More Adapted to Utilize Insoluble Fiber Found in Vegetables***

Researchers also observed a high number of strains in *B. longum* subsp. *longum* isolated from elderly subjects that contain unique genetic information thought to encode extracellular  $\alpha$ -L-arabinofuranosidases (Arabinofuranosidase cluster2 in Fig.2). These enzymes are able to break down complex sugars that are present in plant material, such as vegetables and cereals, all of which contain a high proportion of insoluble fiber.

Elderly Japanese people are reported to eat much more vegetables than younger people<sup>4</sup>, so this genetic trait to digest fiber-containing foods may allow *B. longum* to persist in the elderly gut.

In addition, two clusters of genes indicative of how bacteria respond to environmental stress were found in higher numbers among strains of *B. longum* subsp. *longum* isolated from elderly subjects, including the heat shock protein HSP20.<sup>5</sup> Heat shock proteins are produced to help an organism respond to stress, such as extreme heat, oxygen exposure and starvation. It is reasonable to assume that strains with the ability to respond to stress are better able to adapt and survive.

### ***Certain Strains Have Been Transmitted Between Father and Child, Husband and Wife, and Even Across Three Generations***

Several *B. longum* subsp. *longum* strains, which had been isolated from many different members of the same family, were shown to contain an essentially identical genetic content. This finding suggests that these strains had been transmitted between various family members, not only between mother and child, which has been previously reported.<sup>6</sup>

“It is a remarkable finding that not only was transmission between mother and child observed, but also between father and child and even between husband and wife,” he added. “This is also the first report of a particular strain of gut microbiota that appears to have been transmitted across three generations in a family, for instance, between a grandmother, mother, and infant”, stated Dr. Toshitaka Odamaki, Manager of Microbiota Research Dept. at Next Generation Science Institute of Morinaga and lead researcher of the study.

“We assume this variety of genes and high transfer level of the bacterial species within families is the survival strategy of *B. longum* subsp. *longum* and is key to its wide distribution across the human lifespan,” explained Dr. Odamaki. “This report could provide a promising foundation for future research aimed at identifying the best probiotic candidates at each key life stage,” he continued.

“APC Microbiome Ireland is very interested in how the human microbiota changes over the life stages, in response to exposure to different environmental factors such as habitual diet, antibiotic exposure, and levels of stress”, said Prof Douwe van Sinderen, project leader at APC Microbiome Ireland. He furthermore emphasized the attraction of such a joint scientific effort: “This was a particularly fruitful and gratifying collaborative project with an industry partner, Morinaga, because we were able to join our complementary skills and know-how allowing us to generate insights that we would otherwise not have been able to obtain on our own”.

Dr. Odamaki from Morinaga discussed these findings at the IPA World Congress + Probiota Barcelona held in Barcelona, Spain on February 7th -9th, 2018.

### ***About Morinaga***

Morinaga Milk Industry Co., Ltd. is one of the leading dairy product companies in Japan. Morinaga started research on bifidobacteria in the 1960s, inspired by the fact that bifidobacteria are the predominant bacteria residing in the intestines of breast-fed infants. In 1969, Morinaga isolated its flagship strain *Bifidobacterium longum* BB536 from an infant. Morinaga excels in innovative technology and offers various dairy products and other beneficial functional ingredients to customers around the world.

### **ABOUT APC MICROBIOME IRELAND**

APC Microbiome Ireland (APC; <http://apc.ucc.ie>) is a world leading research institute which was formed in 2003 with funding from Science Foundation Ireland and in conjunction with key industry partners. It represents a seamless collaboration between University College Cork and Teagasc (the Irish Agriculture and Food Development Authority). It is widely recognised that the gut microbiota plays an important role in human health and has become one of the most dynamic, complex and exciting areas of research in both food and pharmaceutical arenas. Over the last decade the APC has established itself as one of the leading global centres in gut microbiota research. The APC has made several landmark discoveries and has published over 1,700

research articles in peer-reviewed journals, generating many journal covers and associated editorials. The APC comprises over 300 individuals, from the scientific Principal Investigators (the APC Faculty) funded by the partner Institutions, the management team, and a dedicated group of research scientists, research assistants and postgraduate students.

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