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学位(専攻分野) 博士(理学)

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学位論文題目 Comparative Analysis of Genus *Bifidobacterium*: Insight into  
its Host Adaptation

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<sup>1</sup>コチュテル(デュアル・ディグリー)

海外の大学との協定に基づき本学に在籍する学生が、同時に相手大学に正規生として在籍し、両大学の教員から共同で学位論文指導を受けるもの。論文完成後、両大学による共同の論文審査に合格した場合は、両大学から単一の学位が授与され、各大学からそれぞれ両大学の共同論文指導によるものである旨を付記した学位記を交付する。

(Form 3)

## Summary of Doctoral Thesis

Name in full Satti, Maria Altaf

Title Comparative Analysis of Genus *Bifidobacterium*: Insight into its Host Adaptation

Human gut is a home to the trillions of microorganisms. Among them many of the bacterial genera impart beneficial effect on host health known as probiotics. Bifidobacteria is amongst one of these health promoting bacteria imparting beneficial health effects on their host by immunomodulation and metabolic activities. The genus *Bifidobacterium* is a ubiquitous, probiotic group in the phylum Actinobacteria, and exist in anaerobic gut environments of various host species, from insects like bees to mammals. The role of these important probiotic genera can be elucidated by understanding their genomics. Now a days with the availability of large sequencing data for these probiotic bacteria deep insights into molecular mechanisms, their interaction with the host and their genetic basis for host adaptability can be made. Comparative analysis of the whole genus of these bacteria can be done to completely understand their adaptation to a diverse host range.

This study comprises of four research projects. The first focuses on providing the accurate annotations and selection of the core genome. The second aims to explore the interaction of bifidobacteria with its host by investigating their extracellular structures. The last two focus on the adaptation of bifidobacteria to diverse host range and elucidate the relationship of bifidobacteria with their host diet.

In the first study, a public library of gene functions in the genus *Bifidobacterium* for its online annotation was prepared. The core genes in each genus were selected based on a newly proposed statistical definition of core genome. Comparative analysis of genus *Bifidobacterium* with another probiotic genus *Lactobacillus* revealed the metabolic characteristics of genus *Bifidobacterium*. The analysis showed that the protein families overrepresented in *Bifidobacterium* were found to be mostly involved in complex sugar metabolism host interaction, and stress responses.

The second study investigate the immunomodulatory role of one of the *Bifidobacterium. bifidum* strain. *B. bifidum* species are among the first colonizer of gastrointestinal tract of the neonates. *B. bifidum* TMC3115 is an important strain isolated from healthy infant. This

strain exhibits inhibitory effect in allergic inflammation. In this study the aim was to explore the genome structure, features and the immunomodulatory role of this strain. The analysis of TMC3115 provided insights into its extracellular structures which might have their role in host interaction and immunomodulation. The study highlights that there is variability among the *Bifidobacterium* genomes just not on species level but also on strain level in terms of host interaction.

The last two studies aim to inspect the relationship between bifidobacteria and its host diet. Bifidobacteria being obligatory anaerobic species, tend to be both host- and niche-specific. The genetic biodiversity of bifidobacteria from bat compared to bifidobacterial species from human and non-human primates was investigated by decoding genome sequences. The investigation of bifidobacterial species from different niches (bat, non-human primates and human being) is fundamental in clarifying repertoire of genes that have caused their evolutionary differentiation. Such genomic analyses support the hypothesis that bat strains have been subjected to genetic adaptations to their host environment such as a peculiar diet heavily based on sugars. Such adaptation of bifidobacterial species is considered relevant to the intestinal microecosystem and hosts' oligosaccharides including those of food and milk. Many species should have co-evolved with their hosts, but the phylogeny of *Bifidobacterium* is dissimilar to that of host animals. The discrepancy could be linked to the niche-specific evolution due to hosts' dietary carbohydrates. This study investigates the relationship between bifidobacteria and their host diet using a comparative genomics approach. Since carbohydrates are the main class of nutrients for bifidobacterial growth, the distribution of carbohydrate-active enzymes, in particular glycoside hydrolases (GHs) that metabolize unique oligosaccharides was examined. When bifidobacterial species were classified by their distribution of GH genes, five groups arose according to their hosts' feeding behaviour. The distribution of GH genes was only weakly associated with the phylogeny of the host animals or with genomic features such as genome size. Thus, the hosts' dietary pattern is the key determinant of the distribution and evolution of GH genes.

[For publication in the SOKENDAI Repository]

## Results of the Thesis Defense

Applicant Name Satti, Maria Altaf

Thesis Title: Comparative Analysis of Genus *Bifidobacterium*: Insight into its Host Adaptation

The Defence Committee, having read candidate's thesis on the activities carried out and her publications, and having listened to the candidate's presentation, expresses its judgment on the basis of the following criteria:

<i>criteria</i>	<i>judgement</i>
Thesis's originality	The work focuses on the relationship between <i>Bifidobacterium</i> strains and their host diets. This research has not been possible without a large number of complete genomes and availability of high performance computing. The combination of computing and microbial systematics is an original, unique part of this study. The work shed new insights into niche adaptation of microbial genomes, and elucidated faster gene shuffling of glyco-genes in <i>Bifidobacterium</i> .
Quality of the methodology adopted	The used methods are based on recent whole-genome comparison and bioinformatics. She has been involved in isolation of multiple new species in <i>Bifidobacterium</i> , and exercised her skill especially on phylogenetics using conserved genes, house-keeping genes, or ribosomal genes. Such skills were fully used in this dissertation work. In addition, the phylogenetic observations were compared with clustering results based on glyco-genes to highlight the correlation between glyco-genes and host diets. This perspective was unique and worth publishing.
Quality of the achieved results	The work discussed whole genome comparison both at the strain level and at the genus level. The comparison was detailed, but more information from metagenomic/microbiome data might assist (or refute) results concluded here. Such complementation from gut microbiome, however, would be hard to be free from sampling biases. For this reason, the current approach focusing on type and well annotated strains is understandable and recommended. The results have been presented in multiple refereed journals over some years, and the scientific soundness and novelty of the work are obvious.
knowledge of the topics dealt with	In her presentation, she could answer questions ranging from molecular phylogeny to niche adaptation clearly. Referees could confirm her scientific knowledge on bacterial species and technical, bioinformatics

	skills clearly. These indicate that the applicant satisfies the criteria for the degree.
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In light of the above, the Defense Committee approves that Ms. Satti, Maria Altaf possesses the sufficient ability to conduct independent research, and unanimously awards the doctoral degree.