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(71) Applicant *(for all designated States except US)*: **SUOMEN PUNAINEN RISTI VERIPALVELU** [FI/FI]; Kivihaantie 7, FI-00310 Helsinki (FI).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WACKLIN, Pirjo** [FI/FI]; c/o Suomen Punainen Risti Veripalvelu, Kivihaantie 7, FI-00310 Helsinki (FI). **MÄTTÖ, Jaana** [FI/FI]; c/o Suomen Punainen Risti Veripalvelu, Kivihaantie 7, FI-00310 Helsinki (FI). **MÄKIVUOKKO, Harri** [FI/FI]; c/o Suomen Punainen Risti Veripalvelu, Kivihaantie 7, FI-00310 Helsinki (FI).

(74) Agent: **KOLSTER OY AB**; Iso Roobertinkatu 23, P.O.Box 148, FI-00121 Helsinki (FI).

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(54) **Title**: USE OF BLOOD GROUP STATUS I

(57) **Abstract**: The present invention relates to a probiotic composition which is tailored based on the spectrum of bifidobacteria found in the intestine of at least one individual with non-secretor blood group phenotype. The present invention further relates to a method of tailoring a probiotic composition based on the bifidobacteria found from the intestine of at least one non-secretor individual.

USE OF BLOOD GROUP STATUS I

Field of the invention

[0001] The present invention relates to a probiotic composition which is tailored based on the spectrum of bifidobacteria found in the intestine of at least one individual with non-secretor blood group phenotype. The present invention further relates to a method of tailoring a probiotic composition based on the bifidobacteria found from the intestine of at least one non-secretor individual. The present invention also relates to use of the secretor status of an individual as a criterion for bifidobacteria-enriched probiotic supplementation. The present invention relates also to method of assessing the need of an individual for bifidobacteria-enriched probiotic supplementation by determining the secretory status of the individual. Also, the invention relates to the use of prebiotics, molecular compounds or additional supportive bacteria strains, to increase the number of, and/or to augment the growth and/or functionality of bifidobacteria in the intestine. Additionally, the invention relates to a probiotic composition for use in treating and/or preventing diseases such as inflammatory bowel disease, diarrhoea, respiratory tract infections, irritable bowel syndrome and/or atopy or allergy.

Background of the invention

[0002] Bifidobacteria comprise the predominant intestinal microbiota in infants and they are adundant also in the adult population comprising up to 10% of the normal intestinal microbiota, although their numbers start to decline in the elderly. An individual is typically colonised with 1-4 bifidobacterial species (Mättö et al. J Appl Microbiol 2004, 98, 459-470). In addition to the individual variation, composition of bifidobacterial species varies between different age groups. *B. longum* biovar *infantis, B. breve* and *B. bifidum* are the most prevalent species in infants and *B. longum* biovar *longum*, *B. adolescentis*, *B. bifidum* and *B. catenulatum* in adults. Variation in the number of bifidobacteria (Mueller et al. Appl Environ Microbiol 2006, 72, 1027-1033) and composition of species (Mättö et al. 2004) between geographic regions has also been reported. Bifidobacteria are generally considered as health promoting bacteria and an increase in bifidobacterial numbers in the intestine is typically used as an end-point in intervention studies with intestinal health-targeted products such as probiotics and prebiotics.

[0003] B*ifidobacterium* spp. strains are used as probiotics. However, due to technological challenges related to stability of the genus, fairly few distinct species and strains, mainly *B. animalis* subps. *lactis,* are available on the current market. Bifidobacteria or bifidobacteria-containing strain mixtures have shown promising results e.g. in alleviation of the symptoms of irritable bowel syndrome (Brenner & Chey, Rev Gastroenterol Disord. 2009 Winter; 9(1):7-15), inflammatory bowel disease (Macfarlane et al. Crit Rev Clin Lab Sci. 2009 46(1), 25-54.), diarrhoea (Chouraqui et al. J Pediatr Gastroenterol Nutr. 2004 Mar; 38(3):242-3), atopic eczema (Yoo et al. Proc Am Thorac Soc (2007) 4, 277-282) and common cold (de Vrese et al. Clin Nutr. 2005 Aug;24(4):479-80). Another challenge in addition to the above-mentioned stability problems, is the fact that a proportion of the study subjects usually have not responded to test probiotics or prebiotics (Fuccio et al., J Clin Gastroenterol 2009, 43, 506-513; Fujimori et al., J. Gastroenterol Hepatol 2007, 22, 1199-1204). These individual are often said to be 'non-responders'. No reason behind the non-responsiviness is known.

[0004] The primary site of colonization of bifidobacteria is the colon, but they are also present in the oral cavity and have been isolated from human milk (Martin et al. Appl Environ Microbiol. 2009, 75(4):965-9). The major energy sources of bifidobacteria are non-digestible dietary carbohydrates and endogenous mucus. They are capable of degrading various oligosaccharides including human milk oligosaccharides and complex carbohydrates present in mucus as substrates. Several bifidobacteria have been shown to adhere to intestinal mucus (He et al. Microbiol Immunol 2001, 45, 259-262). Adhesion of *Bifidobacterium bifidum* to mucus has been shown to increase by supplementation of fucose (Guglielmetti et al. Curr Microbiol. 2009 Aug; 59(2):167-72). The vast variety and spectrum of microbial strains and species in the gut of mammals, including man and the findings demonstrating that the composition of microbial species in the gut will not directly predict their functional outcome, have indicated that predicting the functionality of single probiotic or normal flora species is difficult (Tap et al, Environm Microbiol 2009, 11, 2574-2584). The complexity of the ecosystem is simply too vast. The role of host genetic factors in determining the composition of normal gut microbiota is also poorly understood.

[0005] Binding to blood group antigens has been reported for certain single pathogenic species of bacteria and viruses. In particular, *Helicobacter pylori* binds to the Lewis b (Le^b) antigen in stomach (Boren et al. Science 1993, 262, 1892-1895) and Norovirus binds to ABH ja Le^b antigens (Huang et al. J Virol. 2005 Jun;79(11):6714-22). *Streptococcus pneumoniae* has ability to bind A and B blood group antigens and utilise the glycans (Higgins et al. J Mol Biol. 2009 May 1; 388(2):299-309).

[0006] The blood group antigens are not present in the mucus of all individuals. These individuals, said to have 'non-secretor' blood group, do not have the functional FUT2 gene needed in the synthesis of secreted blood group antigens (Henry et al. Vox Sang 1995; 69: 166-182) and thus they do not secrete ABH antigens in secretions and on mucosa. Those with blood group 'secretor' have the antigens on mucosa. In most populations, the frequency of non-secretor individuals is substantially lower than that of secretor status, about 15-26% of Scandinavians are classified as non-secretors (Eriksson et al. Ann Hum Biol. 1986 May-Jun; 13(3):273-85). The secretor/non-secretor status can be regarded as a normal blood group system and the phenotype can be determined using standard blood banking protocols (Henry et al. 1995). The genotype, that is, the major mutation in the FUT2 gene causing the non-secretor (NSS) phenotype in the European populations (Silva et al. Glycoconj 2010; 27:61-8) has been identified. Non-secretor phenotype has been demonstrated to be genetically associated for example, with an increased risk for Crohn's disease (McGovern et al. Hum Molec Genet 2010; 19(17): 3468-76.), with high vitamin B12 levels in the blood (Tanaka et al Am J Hum Genet 2009; 84:477 – 482), with susceptibility to HI virus infection (Ali et al 2000, J Infect Dis 181: 737-739), with experimental vaginal candidiasis (Hurd and Domino Infection Immunit 2004; 72: 4279- 4281), with an increased risk for asthma (Ronchetti et al. Eur Respir J 2001; 17: 1236 – 1238), with increased risk for urinary tract infections (Sheinfeld et al N Engl J Med 1989; 320: 773 – 777), with an increased risk for ETEC caused diarrhea (Ahmed et al. 2009 Infect Immun. 2009 77(5):2059-64) and with an animal hemorrhagic disease virus (Guillon et al. Glycobiology 2009; 19: 21-28).

Brief description of the invention

[0007] An object of the present invention is a microbial and/or pro-biotic composition which is tailored based on the spectrum of bifidobacteria found in the intestine of at least one individual with non-secretor blood group

phenotype. Another object of the present invention is a method of tailoring a probiotic composition based on the bifidobacteria found from the intestine of at least one non-secretor individual. A further object of the invention is use of secretor blood group status of an individual in assessing the need for bifidobacteria-enriched probiotic supplementation, i.e., as a criterion for bifidobacteria-enriched probiotic supplementation. The present invention relates also to method of assessing the need of an individual for bifidobacteria-enriched probiotic supplementation by determining the secretory status of the individual. Also, an object of the invention is the use of prebiotics, molecular compounds or additional supportive bacteria strains, to increase the number of, and/or to augment the growth and/or functionality of bifidobacteria in the intestine.

[0008] A further object of the present invention is a use of the secretor blood group status of an individual in estimating a dose of bifidobacteria supplementation needed for a desired effect. Another further object of the present invention is to provide a method of identifying an individual at risk for suffering from a gastrointestinal disorder by determining the secretory status of said individual.

[0009] Additional objects of the invention are probiotic compositions for use in treating and/or preventing diseases such as inflammatory bowel disease, diarrhoea, respiratory tract infections, irritable bowel syndrome and/or atopy/allergy. These diseases or disorder are considered to be related to unbalanced mucosal microbiota in an individual.

[0010] The invention is based on the observation that the individuals with non-secretor blood group phenotype have a reduced amount and a reduced diversity of bifidobacteria in their intestinal bacterial population as compared to those with the secretor phenotype. The non-secretor individuals also lack several bifidobacterial species/genotypes present in secretor individuals. In addition, the invention is based on the observation that the bifidobacterial population of the non-secretor individuals show an altered functionality e.g. reduced survival in the harsh conditions in the upper gastrointestinal tract conditions. These observations can be used as a basis for targeted modulation of the bifidobacterial intestinal population in an individual, especially in a non-secretor individual in order to result in the higher diversity and/or amount of bifidobacteria species or strains. In other words, the modulation aims to diversity and/or amount of bifidobacterium in non-secretors that were alike those found typically in secretor individuals. Accordingly, the current in-

vention provides a novel and effective means for optimizing the bacterial, especially bifidobacterial content of a probiotic composition.

[0011] The objects of the invention are achieved by the methods and the uses set forth in the independent claims. Preferred embodiments of the invention are described in the dependent claims.

[0012] Other objects, details and advantages of the present invention will become apparent from the following drawings, detailed description and examples.

Brief description of the drawings

[0013] Figure 1 shows a DGGE gel image of bifidobacterial diversity on faecal samples of 7 non-secretor and 7 secretor individuals. M= marker. Each lane represents a single sample.

[0014] Figure 2 illustrates the three-dimensional PCA plot based on the DGGE analysis of the bifidobacterial profiles.

[0015] Figure 3 illustrates PCA biplot of bifidobacterial DGGE profiles showing the DGGE band positions, which most significantly contributed to the first and the second principal components explaining together 56.3% of the variance. Insert figure indicates the band positions, which contributed the principal component most. Non-secretor samples are indicated with dot, non-secretor with star and samples of unknown secretor status with square.

[0016] Figure 4 illustrates the Shannon diversity Index based on bifidobacterial DGGE profiles test between secretor and non-secretor individuals. P-value for t-test between non-secretor and secretor individuals is shown.

[0017] Figure 5 illustrates the identity of the band positions of Bifidobacteria-DGGE gels based on Blast search of the sequences. The excised and sequenced bands are marked with numbers. The bold letters show band positions, which were either absent or detected rarely in non-secretors. The identity of band positions is shown in the side of the gels with arrows and the colours of the numbers indicate the bands belonging to the same band position and having identical sequences: band position 26.6% (*B. adolescentis*) contains sequenced bands 15, 24, 27 and 29; band position 29.7% (*B. bifidum*) contains sequenced bands 6, 16, 20 and 32; band position 53.5% (*B. longum*) contains sequenced bands 1, 3, 7, 9, 12, 21 and 33; band position 55.0% (*Bifidobacterium sp.*) contains sequenced bands 4 and 18; band position 62.2% (uncultured bifidobacterium) contains sequenced bands 1, 5, 13, 19, 25, 31 and 37; band position 63.7% (*B. catenulatum/pseudocatenulatum*) contains

sequenced bands 22 and 34. Identity of the band positions, which were based on single sequence were following (in black): 8 = Bifidobacterium sp. (*B. catenulatum*), 11= *B. adolescentis,,* 17= uncultured bifidobacterium (*B. ruminantium*), 30= uncultured bifidobacterium (*B. adolescentis*), 36= uncultured bifidobacterium (*B. ruminantium*). The strain name in the parentheses indicates the closest cultivated relative of the sequence, if available.

[0018] Figure 6 shows an image of the normalised DGGE profiles for non-secretor individuals, secretor individuals and individuals with unknown secretor status. Numbers in grey boxes and vertical lines indicate the band positions and star symbol on vertical line indicates that band was binned to the band positions.

[0019] Figure 7 illustrates the PCA plot of bifidobacterial DGGE profiles showing the clustering of the samples from non-secretor (n=14) and secretor (n=57) individuals (left) and the DGGE bands, which most significantly contributed to the first and the second principal components (right). The samples from non-secretor individuals formed separate cluster (indicated by circle) within secretor samples.

[0020] Figure 8 illustrates the bifidobacterial diversity (A) and richness (B) in non-secretor and secretor individuals. Significant differences between non-secretor and secretor individuals in ANOVA are indicated. Samples with no bifidobacterial amplification are excluded from the analysis (one non-secretor individual and six secretor individuals).

[0021] Figure 9 illustrates the detection frequencies (left) and Box and whisker plots (right) of bacteria, bifidobacteria, and bifidobacterial groups in non-secretor (14) and secretor (57) individuals quantified by qPCR. The significant differences between non-secretor and secretors in wilcoxon test are indicated.

Detailed description of the invention

[0022] As bifidobacteria comprise the predominant intestinal microbiota in infants and are adundant also in the adult population, they are considered as essential for maintaining and/or promoting health of an individual. High bifidobacterium diversity in the gut is beneficial for the health of an individual, because bifidobacteria can, for example, prevent adhesion of adverse microbes on gut epithelium and prevent their colonisation in the intestine. They may also modulate the immune response of the host.

[0023] The present invention is based on the finding that the individuals with non-secretor blood group have a reduced amount of bifidobacteria in their intestinal bacterial population. Further, the present invention is based on the finding that the non-secretor individuals have a reduced diversity of bifidobacteria genus and several lacking bifidobacterial species/genotypes in their intestinal bacterial population. Furthermore, the present invention is based on the finding that the bifidobacterial population of non-secretor individuals has an altered functionality e.g. survival in the upper gastrointestinal tract conditions. These findings can be used as a basis for targeted modulation of the bifidobacterial population in the non-secretor individuals and as a criterion for bifidobacteria enriched probiotic supplementation. Further, these findings can be used in designing probiotic compositions targeted for the treatment and/or prevention of diseases such as inflammatory bowel disease, diarrhoea, respiratory tract infections, irritable bowel syndrome and/or atopy/allergy or the symptoms thereof.

[0024] Denaturating Gradient Gel Electrophoresis, DGGE, is a method of choice to detect differences in spectrum or abundance of different bacterial genotypes. In the method, specific PCR primers are designed so that in each experimental setting, only the desired bacterial group or groups are analysed. The differences in band positions and/or their occurrence and/or intensity indicate differences in bacterial compositions between faecal samples. Base composition of the PCR amplified fragment determinates the melting and, thus the mobility of the fragment in the denaturing gradient in gel. The final position of the fragment in gel is consequently specified by the DNA sequence of the fragment, the applied denaturing gradient and the electrophoresis running conditions. The optimised running conditions and denaturing gradient of the gels for the bacterial groups used in this invention are described in Examples. The position of each fragment, the "band position", between different gel runs are normalised by using standards. The band position is indicated relative to length of the gel, the top being 0% and the bottom edge being 100%.

[0025] In connection with the present invention, the terms bacterial genotype and DGGE genotype refer to those strains having the same "band position" in the relevant DGGE analysis. Each genotype or a group of closely-related genotypes can be presented as a "band position". In the present invention, each band position refers to the band positions of the given %-value +/- 1%

unit, i.e. 25.30% refers to any value between 24.30% and 26.30%, when analysed using the methodology described above. It is noted than depending on the exact conditions the nominant %-value can vary; the relative position of the band to the relevant standard is important.

[0026] Bifidobacterium DGGE genotypes that were found to be present at least in one non-secretor individual are listed below in Table 1. The band positions are presented in detail in Figure 6.

Table 1. Bifidobacterium DGGE genotypes that were found to be present at least in one non-secretor individual

Band position	Genotype name
16.3%	Bifidobacterium genotype 4
20.4%	Bifidobacterium genotype 6
22.3%	Bifidobacterium genotype 7
29.7%	*Bifidobacterium bifidum*
43.8%	Bifidobacterium genotype 12
47.3%	Bifidobacterium genotype 16
49.5%	Bifidobacterium genotype 17
55.0%	Bifidobacterium genotype 18
62.2%	Bifidobacterium genotype 20
53.5%	*B. longum*

[0027] Bifidobacterium DGGE genotypes that were found to be present in secretor individuals and absent in non-secretor individuals are listed in Table 2. The band positions are presented in detail in Figure 6.

Table 2. Bifidobacterium DGGE genotypes that were found to be present in secretor individuals and absent in non-secretor individuals

Band position	Genotype name
7.5%	Bifidobacterium genotype 1
3.5%	Bifidobacterium genotype 2
12.6%	Bifidobacterium genotype 3
17.7%	Bifidobacterium genotype 5
24.9%	Bifidobacterium genotype 8
26.6%	*Bifidobacterium adolescentis*
31.2%	Bifidobacterium genotype 9
33.0%	Bifidobacterium genotype 10
39.3%	Bifidobacterium genotype 11

44.5%	Bifidobacterium genotype 13
45.7%	Bifidobacterium genotype 14
46.1%	Bifidobacterium genotype 15
57.3%	Bifidobacterium genotype 19
63.7%	*B.catenulatum/pseudocatenulatum*
69.3%	Bifidobacterium genotype 21

[0028] Based on the DGGE genotypes and isolated strains the inventors were able to identify the bifidobacteria compositions in non–secretor and secretor individuals in more details, that is, to identify the species and diagnostic 16S rRNA nucleotide sequence for band positions. Briefly, the inventors excised the band positions from DGGE gels showing the profiles of faecal samples, sequenced the DNA fragments in the bands and searched for their closest relatives in the sequence databases. In addition, strains isolated from the faecal samples of the non-secretor and secretor individuals were analysed in DGGE in order to screen strains with similar 16S rRNA gene fragment melting behaviour (i.e. sequence) than the observed DGGE bands of faecal samples. Based on the sequences in the DGGE bands and bifidobacterial stains with corresponding band, the bands and further band positions were related to bifidobacterial species. The bifidobacterial species and the diagnostic 16S rRNA fragment sequences of the genotypes detected in non-secretor individuals and only secretor individuals are showed in Tables 3 and 4, respectively.

[0029] Bifidobacterium strains that were found to be present at least in one non-secretor individual are listed below in Table 3.

Table 3. Bifidobacterium strains that were found to be present at least in one non-secretor individual

Identification of the strains	**Sequence 5'->3'**
B. adolescentis (genotype 4)	No sequence. Strains having band in this position (16.3%) have always another band in position 62.2%.
B. adolescentis (genotype 6)	No sequence. Strains having band in this position (20.4%) have always another band in position 26.6%
B. adolescentis (genotype 7)	CTCCAGTTGGATGCATGTCCTTCTGGGAAAGATTCTATCGGTATGGGATGGG GTCGCGTCCTATCAGCTTGATGGCGGGGTAACGGCCCACCATGGCTTCGAC GGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGGGACTGAGATACGGC CCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTGCACAATGGGCGCAAG CCTGATGCAGCGACGCCGCGTGCGGGATGACGGCCTTCGGGTTGTAAACCG (SEQ ID NO:1)

B. catenulatum/ pseudocatenulatum (genotype 8)	No sequence. Strains having band in this position (24.9%) have always another band in position 44.5%.
B. adolescentis	CTCCAGTTGGATGCATGTCCTTCTGGGAAAGATTCATCGGTATGG-GATGGGGTCGCGTCCTATCAGCTTGATGGCGGGGTAACGGCCCAC-CATGGCTTCGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:2)
B. bifidum	TTCCACATGATCGCATGTGATTGTGGGAAAGATTCTATCGGCGTGG-GATGGGGTCGCGTCCTATCAGCTTGTTGGTGAGGTAACGGCTCAC-CAAGGCTTCGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGAGGGATG-GAGGCCTTCGGGTTGTAAACCT (SEQ ID NO:3)
B. dentium (genotype 11)	CTCCGGTTGGATGCATGTCCTTCCGGGAAAGATTCCATCGGTATGG-GATGGGGTCGCGTCCTATCAGCTTGATGGCGGGGTAACGGCCCAC-CATGGCTTCGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGATG-GAGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:4)
B. catenulatum/ pseudocatenulatum (genotype 12)	CTCCGACATGACGCATGTCGTGTTGGGAAAGATTCATCGGTATGG-GATGGGGTCGCGTCCTATCAGGTAGTCGGCGGGGTAACGGCCCACC-GAGCCTACGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:5)
B. catenulatum/ pseudocatenulatum (genotype 13)	CTCCAACATGACGCATGTNGTGTCGGGAAAGATTCATCGGTATGG-GATGGGGTCGCGTCCTATCAGGTAGTCGGCGGGGTAACGGCCCACC-GAGCCTACGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:6)
B. catenulatum/ pseudocatenulatum (genotype 16)	CTCCGACTCCTCGCATGGGGTGTCGGGAAAGATTATATCGGTATGG-GATGGGGTCGCGTCCTATCAGGTAGTCGGCGGGGTAACGGCCCACC-GAGCCTACGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCG (SEQ ID NO:7)
Genotype 17	
B. longum	CTCCAGTTGATCGCATGGTCTTCTGGGAAAGCTTTCGCGGTATGG-GATGGGGTCGCGTCCTATCAGCTTGACGGCGGGGTAACGGCC-CACCGTGGCTTCGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCA-CATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGG-GAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGAGG-GATGGAGGCCTTCGGGTTGTAAACCTC (SEQ ID NO:8)
B. adolescentis (genotype 18)	CTCCGACATGACGCATGTCGTGTCGGGAAAGATTCATCGGTATGG-GATGGGGTCGCGTCCTATCAGCTTGATGGCGGGGTAACGGCCCAC-CATGGCTTCGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:9)

B. adolescentis (genotype 20)	CTCCAGTTGACCGCATGGTCCTCTGGGAAAGCTTTTGCGGTATGG-GATGGGGTCGCGTCCTATCAGCTTGATGGCGGGGTAACGGCCCAC-CATGGCTTCGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTG-CACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:10)
Genotype 21	

[0030] Bifidobacterium strains that were found to be present in secretor individuals and absent in non-secretor individuals are listed in Table 4.

Table 4. Bifidobacterium strains that were found to be present in secretor individuals and absent in non-secretor individuals

Identification of the strains	Sequence 5'->3'
Genotype 2	
Genotype 1	
Genotype 3	
B. adolescentis (genotype 5)	no sequence. Strains having band in this position (17.70%) have always another band in position 26.6% and in 62.2%
Genotype 10	
Genotype 22	
B. adolescentis (genotype 14)	CTCCAGTTGACCGCATGGTCCTCTGGGAAAGATTCATCGGTATGG-GATGGGGTCGCGTCCTATCAGCTTGATGGCGGGGTAACGGCCCAC-CATGGCTTCGACGGGTAGCCGGCCTGAGAGGGCGACCGGCCACATTGG-GACTGAGATACGGCCCAGACTCCTACGGGAGGCAGCAGTGGGGAATATTGCA-CAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:11)
Genotype 15	
Genotype19	
B. catenulatum/ pseudocatenulatum	TGCGGGATGACGGCCTTCGGGTTGTAAACCGCTTTTGATCGGGAG-CAAGCCTTCGGGTGAGTGTACCTTTCGAATAAGCACCGGCTAACTACGTGC-CAGCAGCCGCGGTAATACGTAGGGTGCAAGCGTTATCCGGAATTATTGGGCG-TAAAGGGCTCGTAGGCGGTTCGTCGCGTCCGGTGTGAAAGTCCATCGCT-TAACGGTGGATCTGCGCCGGGTACGGGCGGGCTGGAGTGCGGTAGGGGA-GACTGGAAT (SEQ ID NO:12)
Genotype 23	

[0031] The term 'probiotic' here refers to any bacterial species, strain or their combinations, with health supportive effects, not limited to currently accepted strains or to intestinal effects. The term 'prebiotic' here refers to any compound, nutrient, or additional microbe applied as a single additive or as a mixture, together with probiotics or without probiotics, in order to augment a desired probiotic health effect or to stimulate the growth and

activity of those bacteria in the digestive system which are assumed to be beneficial to the health of the body.

[0032] The present invention relates to a microbial and/or probiotic composition which is tailored based on the spectrum of bifidobacteria found in the intestine of at least one non-secretor individual. Particularly, the present invention relates to a probiotic composition tailored based on the bifidobacterial composition of the intestine of at least one individual with non-secretor blood group phenotype.

[0033] In one embodiment, the microbial or probiotic composition comprises at least one of the strains listed in Table 3. In another embodiment, the probiotic composition comprises two or more of the strains listed in Table 3. Accordingly, optional embodiments of the invention are probiotic compositions comprising for example three, four or five of the strains listed in Table 3. In yet another embodiment, the probiotic composition comprises *Bifidobacterium bifidum* and one or more of the strains listed in Table 3. Accordingly, optional embodiments of the invention are probiotic compositions comprising *Bifidobacterium bifidum* and for example two, three or four of the strains listed in Table 3.

[0034] In a further embodiment, the microbial or probiotic composition of the invention comprises at least one of the strains listed in Table 1. In an even further embodiment, the probiotic composition comprises two or more of the strains listed in Table 1. Accordingly, optional embodiments of the invention are probiotic compositions comprising for example three, four or five of the strains listed in Table 1. In yet further embodiment, the probiotic composition comprises *Bifidobacterium bifidum* and one or more of the strains listed in Table 1. Accordingly, optional embodiments of the invention are probiotic compositions comprising *Bifidobacterium bifidum* and for example two, three or four of the strains listed in Table 1.

[0035] The present invention relates also to a method of tailoring a probiotic composition based on the bifidobacteria found in the intestine of at least one individual with non-secretor blood group phenotype.

[0036] The probiotic composition of the present invention and the probiotic supplement comprising the composition are particularly suitable and effective, but not limited to in use, for the non-secretor individuals for the enhancement of the diversity and numbers of intestinal bifidobacteria. The supplement is based on the rationale that those species of bifidobacteria that can be detected in non-secretors, can also attach themselves to and grow on the

gut, that is, they can colonise the gut. Non-secretors have been reported to be more vulnerable for infections (Blackwell, C.C. 1989. FEMS Microbiology Immunology 47, 341-350). A balanced and diverse population of beneficial Bifidobacteria is, therefore, particularly important for non-secretors.

[0037] In one embodiment of the invention, the probiotic composition or a supplement comprising the composition is tailored for infants of the non-secretor type. In one embodiment of the invention, the probiotic composition or a supplement comprising the composition is tailored for weaning babies or toddlers of the non-secretor type. In another embodiment, the probiotic composition or a supplement comprising the composition is tailored for infants regardless of their secretor phenotype, whose breast-feeding mother is of the non-secretor blood group type. The probiotic composition or a supplement comprising the composition can be used to enhance the development of a balanced intestinal microbiota composition. Babies of non-secretor mothers are more vulnerable to infections, because the milk of the mother does not contain fucosylated glycans, which act as binding locations for pathogens. The diet of babies of non-secretor mothers could be supplemented with fucosylated glycans as prebiotics, together with or without the bifidobacterium composition of the invention. A typical prebiotic ingredient is an oligo/polysaccharide which is non-digestible in the upper parts of the oro-gastrointestinal tract. These oligosaccharides include, but are not limited to, fructo-oligosaccharides or inulin, galacto-oligosaccharides, soy oligosaccharides, resistant starch, and polydextrose. An example shown to be particularly suitable for Bifidobacteria is lacto-N-biose I (Kiyohara et al., Biosci Biotechnol BioChem 2009; 73: 1175-1179). Prebiotics typically are produced by processing from natural sources e.g. from chicory root or milk, alternatively, they may be chemically synthesized. The daily dose needed for a prebiotic effect is typically several grams per day.

[0038] Additionally, in one embodiment, the invention is related to probiotic composition targeted to elderly individuals for supporting the maintenance of bifidobacteria diversity and abundance.

[0039] The present invention relates also to probiotic compositions for use in the treatment and/or prevention of inflammatory bowel disease, diarrhoea, respiratory tract infections, irritable bowel syndrome and/or atopy/allergy.

[0040] In one embodiment, the invention is related to probiotic composition for use in the prevention and/or treatment of inflammatory bowel dis-

ease (IBD) or the symptoms thereof. IBD is an excellent target disease for the invention as not only an altered microbiota composition in the patients has been reported (Sokol et al. Inflamm Bowel Dis. 2006 Feb;12(2):106-11.), but also the therapeutic potential of bifidobacteria-containing probiotic compositions is known (Macfarlane et al. Clin Rev Clin Lab Sci 2009, 46(1), 25-54.). Furthermore, it is established (McGovern et al. Hum Molec Genet 2010; 19(17): 3468-76) that the non-secretor phenotype, i.e. FUT2 gene defect, confers genetic susceptibility to IBD. Hence, it is plausible that the composition according to the present invention is particularly effective in IBD. The treatment can be targeted to a relief of the symptoms and/or to prevention of relapses and/or to increasing the overall quality of life in IBD. It also may be administered together with other currently known drugs for IBD. The composition in one embodiment is targeted to those IBD patients with the non-secretor phenotype.

[0041] In another embodiment, the invention is related to probiotic composition for use in the prevention an/or treatment of microbial infections i.e. diarrhoea and respiratory tract infections as also in these indications therapeutic potential of bifidobacteria-containing probiotics (Chouraqui et al. J Pediatr Gastroenterol Nutr. 2004 Mar; 38(3):242-3; de Vrese et al. Clin Nutr. 2005 Aug;24(4):479-80), and an increased frequency in non-secretor individuals (Ahmed et al. 2009 Infect Immun. 2009 77(5):2059-64; Raza et al. BMJ. 1991, 303(6806):815-8) have been described.

[0042] In one embodiment, the invention is related to probiotic composition for use in the prevention and treatment of irritable bowel syndrome as decreased levels of bifidobacteria (Mättö et al. FEMS Immunol Med Microbiol. 2005 43(2):213-22) and potential of bifidobacteria-containing probiotic products have been described in IBS (Kajander et al. Aliment Pharmacol Ther. 2008 27(1):48-57).

[0043] In yet another embodiment, the invention is related to probiotic composition for use in the prevention of allergy and/or atopy in children. It is established that babies who develop allergy have reduced levels of bifidobacteria in their intestine during the first year of life (Björkstén et al. J Allergy Clin Immunol. 2001 108(4):516-20). Moreover, it has been shown that bifidobacteria are detected in breast milk, and the bifidobacterial species composition in the milk of allergic mothers differs from that of non-allergic mothers (Grönlund et al. Clin Exp Allergy. 2007, 37(12):1764-72). Bifidobacteria-

containing probiotic products have shown potential in prevention of atopic eczema (Yoo et al. Proc Am Thorac Soc (2007) 4, 277-282).

[0044] The probiotic compositions and supplements so designed may have beneficial effects on the health and/or well-being of a human and may be in the form of, for example, a food product, capsule, tablet or powder. The composition can be formulated into a product of dairy or beverage industry, a functional food product or a nutritional supplement as well as a capsule, emulsion, or powder.

[0045] A typical probiotic ingredient is freeze-dried powder containing typically 10^{10}–10^{12} viable probiotic bacterial cells per gram. In addition it normally contains freeze drying carriers such as skim milk, short sugars (oligosaccharides such as sucrose or trehalose). Alternatively, the culture preparation can be encapsulated by using e.g. alginate, starch, xanthan as a carrier. A typical probiotic supplement or capsule preparation contains approximately 10^{9}–10^{11} viable probiotic bacterial cells per capsule as a single strain or multi-strain combination.

[0046] A typical probiotic food product, which can be among others fermented milk product, fermented milk-based product or juice, contains approximately 10^{9}–10^{11} viable probiotic bacterial cells per daily dose. Probiotics are incorporated in the product as a probiotic ingredient (frozen pellets or freeze dried powder) or they are cultured in the product, such as yogurt, curd and/or sour milk, during fermentation.

[0047] Bifidobacteria containing composition or supplement contains optionally also at least one prebiotic optimised for the growth stimulation of the selected *Bifidobacterium* strain or strains. The addition of a prebiotic to the composition of the present invention is to further augment the efficacy of the probiotic composition by helping the survival of those Bifidobacterium spieces added into the composition but not commonly found in an individual.

[0048] The present invention provides also means for tailoring and/or optimising or potentiating an existing probiotic and/or synbiotic product with at least one bifidobacterial strain selected according to the present invention to improve the responsiveness and/or effect of the product in non-secretors.

[0049] The present invention also relates to a use of the secretory status of an individual in assessing the need for bifidobacteria-enriched probiotic supplementation. The present invention also relates to a method of as-

sessing the need of an individual for bifidobacteria-enriched probiotic supplementation by determining the secretory status of the individual.

[0050] The present invention further relates to a use of the secretory status of an individual in estimating a dose of bifidobacteria supplementation needed for a desired effect. Typically individuals of non-secretor phenotype should need higher doses of probiotics than those with the secretor phenotype.

[0051] The present invention also relates to a method of identifying an individual at risk for suffering from a gastrointestinal disorder by determining the secretory status of said individual. The status can be determined, for example, from a sample of saliva, using standard blood grouping methods or from the genomic DNA of an individual by determining adequate mutations in the FUT2 gene (Silva et al. Glycoconjugate Journal 2009, DOI 10.1007/s10719-009-9255-8).

[0052] Stabilization of the intestinal bacterial population, especially bifidobacterial population, has been observed to be delayed after microbiota disturbances (Mättö et al. 2008). Thus, the present invention provides a use of the secretor status and bifidobacterial species diversity of an individual in following the microbiota stabilisation after such drastic disturbances.

[0053] The results of the present invention indicated that non-secretors had lower bifidobacterial diversity in the intestine than secretor individuals. Among strains of *Bifidobacterium* there were strains that were more common in the intestine of non-secretors. The non-secretors lacked or carried very low or undetectable numbers of several *Bifidobacterium* genotypes (e.g. genotypes of strains *B. adolescentis* and *B. catenulatum/pseudocatenulatum),* which were common in secretors (Table 4). Moreover, *B. bifidum*, and certain *B. adolescentis* and *B. catenulatum/pseudocatenulatum* genotypes, were present more rarely in non-secretor than in secretor individuals (Table 3 and 6). Of the most frequently detected bifidobacterial strains, only *B. longum* was equally common in both secretor and non-secretor individuals. Accordingly, some bifidobacteria are present in GI tract of almost all humans, but non-secretors miss some or many of the bifidobacterial strains i.e. all human share some bifidobacterial species, but non-secretors miss many bifidobacterial species present commonly in secretors. Based on these findings, the probiotic composition and/or supplement of the present invention contain in particular those bifidobacterial species abundant in individuals with non-secretor phenotype.

[0054] The invention will be described in more detail by means of the following examples. The examples are not to be construed to limit the claims in any manner whatsoever.

EXAMPLES

Materials and methods

[0055] The materials and methods described herein are common to examples 1 to 7.

[0056] 59 healthy adult volunteers (52 females and 7 males) we recruited to the study. Both faecal and blood samples were collected from 59 volunteers. The age of the volunteers ranged from 31 to 61 and was in average 45 years.

[0057] Faecal samples were frozen within 5 hours from defecation. DNA from 0.3 g of faecal material was extracted by using the FASTDNA® SPIN KIT FOR SOIL (Qbiogene). Partial bifidobacterial 16S rRNA gene was amplified by PCR with bifidobacterial specific primers Bif164F and Bif662R+GC (Satokari et al., Appl Environm Microbiol 2001, 67, 504-513). The specificity of the primers was tested with *Bifidobacterium* strains (*B.adolescentis* E-981074, *B. bifidum* E-97795, *B. lactis* E-97847, *B. longum* E-96666, *B. angulatum* DSM 20098 and *Bifidobacterium catenulatum* DSM 16992), which are the most common *Bifidobacterium* species inhabiting human gut, as well as 43 other bacterial strains having representatives of common human cut bacteria. Amplified PCR fragments were separated in 8% DGGE gel with denaturing gradient from 45% to 60%. DGGE gels were run at 70 V for 960 mins. DGGE gels were stained with SYRBSafe for 30 mins and documented with SafeImager Bluelight table (Invitrogen) and AplhaImager HP (Kodak) imaging system.

[0058] Digitalised DGGE gel images were imported to the Bionumerics-program version 5.0 (Applied Maths) for normalisation and band detection. Bands were normalised with marker samples constructed from bifidobacterial strains. Band search and bandmatching was performed as implemented in Bionumerics. Bands and bandmatching were manually checked and corrected.

[0059] The bands were excised from bifidobacteria-DGGE gels. DNA from bands was eluted by incubating bands in 50 µl sterile H_2O at +4°C overnight. The correct position and purity of only each of the excised bands

were tested by amplifying DNA in bands and running the amplified fragments along the original samples in DGGE. Bands, which only produced single bands and were in the correct position in the gels, were sequenced in Eurofins MWG (Germany). The sequences were trimmed, manually checked and corrected for ambiguous bases and aligned by ClustalW. The closest relatives of the sequences were searched using Blast and NCBI nr database. Distance matrix of the aligned sequences was used to compare the similarity of the sequences.

EXAMPLE 1

[0060] Secretor status was determined from the blood samples using the standard in-house blood grouping protocols of Finnish Red Cross Blood Service. Secretor status was determined from 59 individual and 48 were secretors and seven were non-secretors. For 4 samples, secretor status was could not be determined.

EXAMPLE 2

[0061] DGGE analysis targeted for the faecal bifidobacterial population was performed as described above in the material and methods. DGGE gel images showed fewer numbers of bands in the samples obtained from the non-secretor individuals than in the samples from secretor individuals, indicating that fewer bifidobacterial genotypes were present in non-secretor than in secretor individuals. In average, non-secretors had 2.5 (maximum 4) bands and secretors 5.2 bands (maximum 11 bands) in bifidobacterial DGGE profiles. In five samples bifidobacteria were not detected (one non-secretor sample and 4 secretor samples). The Bifidobacterial profiles of all non-secretor individuals and selected bifidobacterial profiles of the secretor individuals are presented in Figure 1.

EXAMPLE 3

[0062] DGGE analysis targeted for the faecal bifidobacterial population was performed as described above. Principal component analysis (PCA) was performed as implemented in the Bionumerics software package. PCA based on intensities of bands detected by DGGE, was used to ordinate samples and to find out the bands which predominantly contributed to the principal components. Images of DGGE gels were analysed using the Bionumerics to allow statistical analysis between samples. PCA based on intensities of bands in DGGE gels showed grouping of the samples obtained from the non-

secretors. The first and second principal component explained of the 56.3% of the total variance. The results are presented in Figure 2.

EXAMPLE 4

[0063] DGGE analysis targeted to the faecal bifidobacterial population was performed as described above. PCA based on intensities of bands detected by bifidobacterial DGGE was used to ordinate samples and to find out the bands which most contributed to the principal components. In the PCA biplot, the first and second principal component contributed 56.3% of the total variance. The bands in positions 26.6%, 53.3%, 62.2% and 63.7% contributed most clearly to the components. These bands were the most commonly detected bands in the samples (Table 5). The PCA biplot based on bifidobacterial DGGE profiles is presented in Figure 3.

EXAMPLE 5

[0064] DGGE analysis targeted for the faecal bifidobacterial population was performed as described above. The Shannon diversity index based on band intensities was used to summarise the diversity of bifidobacteria in the samples. The index calculations and t-tests were done. The Shannon index, which describes diversity based on abundance and eveness of species, showed that bifidobacterial diversity was statistically significantly reduced in non-secretor individuals in comparison to secretor individuals ($p = 0.009$). Thus, non-secretor individuals have lower bifidobacterial diversity than secretor individuals. The results are presented in Figure 4.

EXAMPLE 6

[0065] DGGE analysis and identification of the bands by sequencing was performed as described above. Identification was based on the Blast search of the sequences obtained from the excised bands of the DGGE gels. The results showed that several common bifidobacterial genotypes were missing or were present rarely in non-secretor individuals as compared to those found in secretor individuals. Specifically, most commonly detected genotypes of *B. adolescentis* (bands 15, 24, 27, and 29 in Figure 5) and *B. catenulatum/pseudocatenulatum* (bands 22 and 34 in Figure 5) and genotypes related to uncultured *Bifidobacterium* (bands 5, 13, 19, 25, 31 and 37 in Figure 5), or those spieces and/or strains of *Bifidobacterium* whose detailed identification at the spieces-level requires further analyses, e.g. sequencing, were not detected

in non-secretors. Moreover, genotypes related to *B. bifidum* (bands 6, 8, 11, 16, 17, 20, 30, 32, 36 in Figure 5) and uncultured *Bifidobacterium* were more rarely detected in non-secretor individuals than in secretor individuals. The most commonly detected *Bifidobacterium* genotypes in the entire set of study samples were also those whose occurrence differed between the non-secretor individuals and secretor individuals (bold in Table 5), except for *B. longum* which was equally common in both secretor individuals and non-secretor individuals. Thus, the results indicated that non-secretors lacked or carried a low number of several *Bifidobacterium* genotypes, which were common in secretors. The results are presented in Figure 5 and Table 5.

EXAMPLE 7

[0066] DGGE analysis and band position analysis using the BioNumerics-software were performed as described above. The result showed that the *Bifidobacterium* genotypes present in the nonsecretor individuals represented *Bifidobacterium* genotype 4 (band position 16.3%), *Bifidobacterium* genotype 6 (band position 20.4%), *Bifidobacterium* genotype 7 (band position 22.3%), *Bifidobacterium bifidum* (band position 29.7%), *Bifidobacterium* genotype 12 (band position 43.8%), *Bifidobacterium* genotype 16 (band position 47.3%), *Bifidobacterium* genotype 17 (band position 49.5%), *Bifidobacterium* genotype 18 (band position 55.0%), *Bifidobacterium* genotype 20 (band position 62.2%) and *Bifidobacterium longum* (band position 53.5%). (Table 5, Figure 6).

Table 5. The identification of the band positions and the detection frequency of bands in non-secretors (NSS, n=6) and secretors (SS, n=42). The band positions, which frequency differed between non-secretors and secretors are in bold. (nd = not determined) *The sequences of two bands classified in to this band position (43.8%) were not identical and they had similarity 97.3%.

Closest relative by Blast (closest cultured relative, similarity in Blast)	Number of sequenced bands	Band position	Total number of bands detected	% in NSS	% in SS	% in all
B. longum	*7*	**53.5%**	47	83	88	87
[0198] *B. adolescentis a*	***4***	***26.6%***	***36***	***0***	***775***	***667***
[0202] *uncultured Bifidobacterium (B. adolescentis, 475/480, 98%)*	***6***	***62.2%***	***34***	***333***	***667***	***663***
Nd		***17.7%***	***18***	***0***	***338***	***333***
[0210] *B. catenulatum/ pseudocatenulatum*	***2***	***63.7%***	***18***	***0***	***338***	***333***
Nd		***20.4%***	***16***	***117***	***331***	***330***
B. bifidum	***4***	***29.7%***	***16***	***117***	***331***	***330***
B. adolescentis b	*1*	*22.3%*	*10*	*117*	*119*	*119*
Bifidobacterium sp (B. catenulatum, 477/479, 99%)		*47.3%*	*9*	*117*	*117*	*117*
*uncultured Bifidobacterium (B. adolescentis 476/481, 98%, /B. ruminantium 455/457, 99%)**		*43.8%*	*8*	*117*	*115*	*115*
uncultured Bifidobacterium (B. adolescentis 465/468,99%)		*55.0%*	*7*	*117*	*113*	*113*
[0243] *uncultured Bifidobacterium (B. ruminantium 454/456, 99%)*		***44.5%***	***6***	***0***	***113***	***111***
Nd		*16.3%*	*5*	*17*	*8*	*9*
Nd		***46.1%***	***5***	***0***	***10***	***9***
[0249] *Other (11 band positions)*			*1...4*	*00-17%*	*22-8%*	*22-7%*

EXAMPLE 8

[0067] In this example number of volunteers was increased to 71 by recruiting 12 new volunteers in comparison to 59 volunteers in previous examples 1-7. For these 71 volunteers, in addition to phenotyping, secretor status was genotyped by sequencing the coding exon of FUT2 as described in Silva et al. (Silva et al. Glycoconj J 2010, 27, 61-68) and Ferrer-Admetlla et al. (Mol Biol Evol 2009, 26, 1993-2003). Genotyping of FUT2 exon allowed de-

termination of secretor status for the Lewis negative individuals, whose phenotypic secretor status could not be determined. The DGGE analysis targeted to the faecal bifidobacterial population and data-analysis were performed as described above, except that in PCA on presence and absence of bands was used. Statistical analyses, Anova, were computed with statistical programming language R, version 2.10.1.

[0068] In the enlarged dataset (n=71), 57 individuals represented secretors and 14 represented non-secretors. Similarly to the PCA results in examples 3 and 4, non-secretor individuals formed a separate cluster within secretor individuals in PCA analysis of bifidobacterial DGGE profiles. The PCA biplot based on bifidobacterial DGGE profiles is presented in Figure 7. The observed clustering in PCA indicates that bifidobacterial population was altered in non-secretor individuals in comparison to the secretor individuals. These results confirmed the earlier result performed with smaller number of samples (see examples 3 and 4).

[0069] Band positions that mostly contributed to the PCA clustering were (17.7%, 20.4%, 26.6%, 62.2% and 63.7% (Figure 7). These band positions were also among the most commonly detected in secretor individuals (Table 6). The band positions 17.7% (*B. adolescentis*) and 63.7% (*B. catenulatum/pseudocatenulatum*) were missing in all non-secretor individuals and all the other common band positions (present in >10% of the samples), expect the band position 53.5% related to *B. longum,* were clearly less frequently detected in non-secretor individuals than in secretor individuals (Table 6). The band positions associated to the secretor status were related to *B. adolescentis*, *B. catenulatum/pseudocatenulatum*, *B. dentium* and *B. bifidum*. Thus, the results indicated that non-secretors lacked or carried rarely several *Bifidobacterium* genotypes, which were common in secretors.

[0070] Similarly to the example 5, the Shannon diversity index based on band intensities was used to summarise the diversity of bifidobacteria in the samples. In addition, number of bands was used to summarise the bifidobacterial species richness in the samples. The increased number of volunteers confirmed that diversity is reduced in non-secretor individuals. The Shannon diversity index and number of bands showed that bifidobacterial diversity and richness was statistically significantly reduced in non-secretor individuals in comparison to secretor individuals ($p = 0.0001$ and 0.0003, respectively). In average, non-secretor individuals had almost two times (1.9) more

bands per sample than secretor individuals. In average, non-secretor individuals had 2.5 (maximum 5) bands and secretor individuals 4.7 bands (maximum 11 bands) in bifidobacterial DGGE profile. Thus, non-secretor individuals have lower bifidobacterial diversity and richness than secretor individuals. The results are presented in Figure 8.

Table 6. Identification of the band positions of Bifidobacterial DGGE by sequencing and the detection frequencies of the bands in secretor (14) and non-secretor individuals (57).

*Identification by sequencing**	Band position	Hits	% in non-secretors	% in secretors
B. longum	53.5%	56	79	79
B. adolescentis	62.2%	41	50	60
B. adolescentis	26.6%	40	14	67
	17.7%	18	0	32
B. catenulatum/pseudocatenulatum	63.7%	18	0	32
B. bifidum	29.7%	17	7	28
	20.4%	16	7	26
B. adolescentis	22.3%	13	14	19
B. catenulatum/pseudocatenulatum	43.8%	13	14	19
B. catenulatum/pseudocatenulatum	47.3%	9	7	14
B. adolescentis	55.0%	9	7	14
B. catenulatum/pseudocatenulatum	44.5%	8	7	12
	39.3%	7	7	11
	16.3%	5	7	7
	46.1%	5	0	9
	24.9%	4	7	5
	3.5%	3	0	5
B. adolescentis	45.7%	4	0	7
	12.6%	3	0	5
	33.0%	3	0	5
	49.5%	3	7	4
	69.3%	3	7	4
	7.5%	1	0	2
	36.4%	1	0	2
	57.3%	1	0	2
	64.8%	1	0	2

* The similarity of the partial 16S rDNA sequence (475-490 bp) to the type strain of the indicated species was ≥ 98%.

EXAMPLE 9

[0071] qPCR method was applied to detect and quantify the 16S rRNA gene copies of bacteria, bifidobacteria and 4 bifidobacterial groups/species, *B. bifidum*, *B. longum* group, *B. catenulatum/pseudo-catenulatum* and *B. adolescentis* in faecal samples of non-secretor individuals (n=14) and secretor individuals (n=57). The primers and annealing temperature for each primer pair is shown in table 5. For each primer pair reaction mixture (25 µl) was composed of 0.3 µM of each primer (Sigma-Aldrich, UK), 1 x Power SYBR Green PCR Master Mix (Applied Biosystems, CA, USA), 4 µl faecal DNA diluted to the concentration of 1 ng/µl for bifidobacterial group-specific primers and to the concentration of 0.1 ng/µl for universal and bifidobacterial primers. The amplification conditions in ABI Prism 7000 instrument (Applied Biosystems, CA, USA) were one cycle of 95 °C for 10 mins, followed by 40 cycles of 95 °C for 15 s, and appropriate annealing temperature (see table 6) for 60 s. Melting temperature curves from 60°C to 95°C were analysed to determine the specificity of the amplification. All the samples and standards were analysed in three replicates. Standard curves for each detected bacterial groups were constructed from the corresponding bacterial strain (Table 7) by using 10-fold dilutions of known concentrations of bacterial genomic DNA (from 10 ng/µl to 0.0004 ng/µl). Genomic DNA from standard strains was extracted by QIAmp®DNA mini kit (Qiagen) combined with cell lysis in the FastPrep® Instrument (MP Biomedicals, CA, USA). GenEx Enterprise v.5.2.6.34 (MultiD Analyses AB, Sweden) was used for analysis of standard curves and reverse quantification of the samples. Statistical analyses, Wilcoxon tests, were computed with statistical programming language R, version 2.10.1.

Table 7. The primers targeting the 16S rRNA gene, annealing temperature and the strains used as standards for qPCR.

Group	Primer	Primer sequence 5'→3'	An-neal-ing-T	Standard strain	
Bifidobacteria	qBifF qBifR[2]	TCGCGTCYGGTGTGAAAG CCACATCCAGCRTCCAC	59	*B. bifidum* (NCIMB41171)	E-97795
B. longum group*	BiLON-1 BiLON-2[3]	CAGTTGATCGCATGGTCTT TACCCGTCGAAGCCAC	62	*B. longum* (ATCC15707)	E-96664
B. bifidum	BiBIF-1 BiBIF-2[3]	CCACATGATCCATGTGATTG CCGAAGGCTTGCTCCCAAA	58	*B. bifidum* (NCIMB41171)	E-97795
B. catenulatum/ pseudocatenulatum	BiCATg-1 BiCATg-2[3]	CGGATGCTCCGACTCCT CGAAGGCTTGCTCCCGAT	62	*B. catenulatum* DSM 16992	
B. adolescentis group	BiADOg-1a BiADOg-1b BiADO-2[3,**]	CTCCAGTTGGATGCATGTC TCCAGTTGACCGCATGGT CGAAGGCTTGCTCCCAGT	58	*B. adolescentis* E-981074 (ATCC15703)	

*Amplifies species *B. longum*, *B. infantis, B. suis*. **Two forward primers to amplify *B. adolescentis* genotypes A and B. References: [1] Tseng et al. Clin Chem 2003, 49, 306-309. [2] Rinttilä et al. J Appl Microbiol 2004, 97, 1166-1177. [3] Matsuki et al. Appl Environ Microbiol 2004, 70, 167-173.

[0072] Bifidobacteria were detectable in over 90% of the samples in both non-secretor and secretor individuals (Figure 9). Total amount of bifidobacteria was lower (p=0.05) and fewer bifidobacterial species were present in non-secretor individuals in comparison to secretor individuals (Figure 9). All the bifidobacterial groups were detected less frequently in non-secretor than in secretor individuals, confirming the DGGE results. *B. bifidum* was detected in 14% of the non-secretor samples (compare 35% of the secretor samples), *B. catenulatum/pseudocatenulatum* in 29% of the non-secretor samples (compare 47% of the secretor samples) and *B. adolescentis* in 57% of the non-secretor samples (compare 75% the secretor samples). Moreover, in samples with detectable amounts of *B. adolescentis* group, the abundance of the *B. adolescentis* was lower in non-secretor than in secretor individuals (p=0.055) (Figure 9).

EXAMPLE 10

[0073] We isolated bifidobacterial strains from the non-secretor and secretor individuals and analysed their 16S rRNA gene fragments in DGGE gel along with faecal samples in order to find the strains corresponding the observed DGGE band positions (i.e. genotypes). Strains were isolated by applying TNO TIM-1 model, which mimics conditions in stomach and small intestine.

Faecal slurries were prepared from pooled non-secretor samples (total 12.1 g faeces), two individual samples of non-secretors (1.9 and 2 g of faeces) and pooled secretor samples (total 9.8 g of faeces). The same faecal samples were used in the DGGE analysis and strain isolation. Faecal slurries for TIM-1 acquired by mixing faeces with artificial saliva and sterile water/milk were used as input for the TIM-1 model. Two states of the model were applied: In one state, T1/2 for emptying the gastric content was set to 20 min, pH change from pH 2.0 to 1.7 in 30 min and level of gastric secretion on 20%. In another state, gastric emptying halftime was set 30 min, gastric pH decrease from 5.0 to 1 .8 in 90 min and level of gastric secretion to 100%. The gastric content was passed into the duodenal compartment, where it was neutralized to pH 6.4, and bile and pancreatin were added, followed passage (time 10 minutes) into the jejunum compartment and into the ileum compartment. In each compartment the physiological concentrations of bile salts, pancreatic enzymes and electrolytes simulated in combination with an average physiological passage through the small intestine. The samples were collected from after 120-180, 180-240 and 240-300 mins treatment in model and bifidobacterial isolated using beerens and RB (raffinose bifidobacterial media) media. The isolates were incubated in anaerobic conditions for 72 hours at 37 °C. The strains from faecal samples of secretor individuals were also isolated from faecal slurries by plating directly on beerens agar and incubating in anaerobic conditions for 72 hours at 37 °C. The isolates were screened with RAPD using primers OPA-2 as described in Mättö et al. (J Appl Microbiol 2004, 98, 459-470). The strains representing different RAPD profiles were deposit to culture collection of Finnish Red Cross Blood service and analysed in DGGE to find the band positions they correspond. Genomic DNA from strains was extracted by QIAmp®DNA mini kit (Qiagen) combined with cell lysis in the FastPrep® Instrument (MP Biomedicals, CA, USA). The strains were identified by sequencing of the 16S rRNA gene fragment (~700 bp). DGGE analysis was performed as described above.

[0074] Total of 274 Bifidobacterial strains from non-secretor individuals and 360 strains from secretor individuals were isolated. The isolates were screened with RAPD for detection of different bifidobacterial strains. In RAPD screening of isolates, 15 different bifidobacterial isolates owing different RAPD profiles originated from non-secretor individuals and 28 bifidobacterial isolates originated from secretor individuals.

[0075] Strains corresponded 15 of the total 26 band position detected in the DGGE profiles of the faecal samples. Moreover, the strains corresponded to almost all common bifidobacterial DGGE genotypes (12 of the 13 strains present > 10% samples) (Table 6). The corresponding strains from non-secretor individuals were found for 6 DGGE band positions, whereas corresponding strains from secretor individuals were found for 13 DGGE band positions. The bifidobacterial band positions/genotypes, sequences of the positions and their corresponding strains in the DGGE are listed in Table 8. Some strains have several 16S rRNA copies and thus one strain may correspond to several band positions.

Table 8. The sequences and identification of bifidobacterial band positions in DGGE and the presence of corresponding strains from secretor and non-secretor individuals. The sequence for the 16S rRNA gene fragment, that is amplified and analysed in DGGE with primers Bif164F and Bif662R, is showed for each position. Bifidobacterial genotype number refers to the genotype in Table 1 and 2.

Band position	Strains from secretors	Strains from non-secretors	Identification of the strains	Sequence 5'->3'
16.3%	+	+	*B. adolescentis* (genotype 4)	no sequence . Strains having band in this position have always another band in position 62.2%.
17.7%	+	-	*B. adolescentis* (genotype 5)	no sequence. Strains having band in this position have always another band in position 26.6% and in 62.2%
20.4%	+	-	*B. adolescentis* (genotype 6)	no sequence Strains having band in this position have always another band in position 26.6.2%
22.3%	+	+	*B. adolescentis* (genotype 7)	CTCCAGTTGGATGCATGTCCTTCTGGGAAAGATTCTATCGGTATGGGATGGGGTCGCGTCC-TATCAGCTTGATGGCGGGGTAACGGCCCACCATGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCG (SEQ ID NO:1)

24.9%	+	-	*B. catenulatum/ pseudocatenulatum* (genotype 8)	no sequence Strains having band in this position have always another band in position 44.5%
26.6%	+	-	*B. adolescentis*	CTCCAGTTGGATGCATGTCCTTCTGGGAAAGATTCATCGGTATGGGATGGGGTCGCGTCC-TATCAGCTTGATGGCGGGGTAACGGCCCACCATGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:2)
29.7%	+	-	*B. bifidum*	TTCCACATGATCGCATGTGATTGTGGGAAAGATTCTATCGGCGTGGGATGGGGTCGCGTCC-TATCAGCTTGTTGGTGAGGTAACGGCTCACCAAGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGAGGGATG-GAGGCCTTCGGGTTGTAAACCT (SEQ ID NO:3)
39.3%	+	-	*B. dentium* (genotype 11)	CTCCGGTTGGATGCATGTCCTTCCGGGAAAGATTCCATCGGTATGGGATGGGGTCGCGTCC-TATCAGCTTGATGGCGGGGTAACGGCCCACCATGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGATG-GAGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:4)

43.8%	+	-	*B. catenulatum/ pseudocatenulatum* (genotype 12)	CTCCGACATGACGCATGTCGTGTTGGGAAAGATTCATCGGTATGGGATGGGGTCGCGTCC-TATCAGGTAGTCGGCGGGGTAACGGCCCACCGAGCCTACGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:5)
44.5%	+	-	*B. catenulatum/ pseudocatenulatum* (genotype 13)	CTCCAACATGACGCATGTNGTGTCGGGAAAGATTCATCGGTATGGGATGGGGTCGCGTCC-TATCAGGTAGTCGGCGGGGTAACGGCCCACCGAGCCTACGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:6)
45.7%	+	-	*B. adolescentis* (genotype 14)	CTCCAGTTGACCGCATGGTCCTCTGGGAAAGATTCATCGGTATGGGATGGGGTCGCGTCC-TATCAGCTTGATGGCGGGGTAACGGCCCACCATGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:11)
47.3%	-	+	*B. catenulatum/ pseudocatenulatum* (genotype 16)	CTCCGACTCCTCGCATGGGGTGTCGGGAAAGATTATATCGGTATGGGATGGGGTCGCGTCC-TATCAGGTAGTCGGCGGGGTAACGGCCCACCGAGCCTACGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCG (SEQ ID NO:7)

53.5%	+	+	*B. longum*	CTCCAGTTGATCGCATGGTCTTCTGGGAAAGCTTTCGCGGTATGGGATGGGGTCGCGTCC-TATCAGCTTGACGGCGGGGTAACGGCCCACCGTGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGAGGGATG-GAGGCCTTCGGGTTGTAAACCTC (SEQ ID NO: 8)
55.0%	-	-	*B. adolescentis* (genotype 18)	CTCCGACATGACGCATGTCGTGTCGGGAAAGATTCATCGGTATGGGATGGGGTCGCGTCC-TATCAGCTTGATGGCGGGGTAACGGCCCACCATGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:9)
62.2%	+	+	*B. adolescentis* (genotype 20)	CTCCAGTTGACCGCATGGTCCTCTGGGAAAGCTTTTGCGGTATGGGATGGGGTCGCGTCC-TATCAGCTTGATGGCGGGGTAACGGCCCACCATGGCTTCGACGGGTAGCCGGCCTGA-GAGGGCGACCGGCCACATTGGGACTGAGATACGGCCCAGACTCCTACGGGAGGCAG-CAGTGGGGAATATTGCACAATGGGCGCAAGCCTGATGCAGCGACGCCGCGTGCGGGAT-GACGGCCTTCGGGTTGTAAACCGC (SEQ ID NO:10)
63.7%	+	+	*B. catenulatum/ pseudocatenulatum*	TGCGGGATGACGGCCTTCGGGTTGTAAACCGCTTTTGATCGGGAGCAAGCCTTCGGGT-GAGTGTACCTTTCGAATAAGCACCGGCTAACTACGTGCCAGCAGCCGCGGTAATACG-TAGGGTGCAAGCGTTATCCGGAATTATTGGGCGTAAAGGGCTCG-TAGGCGGTTCGTCGCGTCCGGTGTGAAAGTCCATCGCTTAACGGTGGATCTGCGCCGGG-TACGGGCGGGCTGGAGTGCGGTAGGGGAGACTGGAAT (SEQ ID NO:12)

EXAMPLE 11

[0076] The survival of bifidobacteria in TNO TIM-1 model treatment was analysed by counting of viable bacteria before and after treatment as described in example 10. For the analysis of bifidobacterial survival in TNO TIM-1 model, faecal slurries were prepared from pooled non-secretor samples (total 12.1 g faeces) and secretor samples (total 9.8 g of faeces) were used. Samples were collected from faecal slurries before the TIM-1 treatment (intake samples) and after 120-180 mins, 180- 240 mins, and 240-300 mins treatments. Dilution series of collected samples were plated in duplicate on beerens and RB media and incubated for 72 hours at 37 °C.

[0077] The survival of bifidobacteria from secretor pool was 2.4 (RB agar) or 32 (Beerens agar) times higher than the survival of bifidobacteria from non-secretor pool (Table 9). These results indicated that cultivable bifidobacterial population in non-secretor individuals differed from bifidobacterial population in secretor individuals. Furthermore, the bifidobacterial population in non-secretor individuals seemed to be less tolerant for the harsh conditions of TNO TIM-1 model, mimicking stomach and small environments.

Table 9. The survival of bifidobacteria from pooled faecal samples of secretor and non-secretor individuals in the TIM-1 model (upper gastrointestinal tract conditions). Viability was determined by plate count culturing using Beerens and RB media.

	Secretor pool		Non-secretor pool	
	Beerens	RB	Beerens	RB
Intake, total cfu in sample	6,5E+08	3,4E+09	4,1E+08	3,2E+09
Total survival , total cfu in samples	2,1E+07	1,6E+08	5,5E+05	6,4E+07
% survival	3,2	4,8	0,1	2,0

CLAIMS

1. A probiotic composition characterized in that it is tailored based on the bifidobacterial composition of the intestine of at least one individual with non-secretor blood group phenotype.

2. The probiotic composition according to claim 1, characterized in that it comprises at least one of the strains listed in Table 3.

3. The probiotic composition according to claim 2, characterized in that it comprises *Bifidobacterium bifidum*, together with at least one of the strains listed in Table 3.

4. The probiotic composition according to claim 1, characterized in that it comprises at least one of the strains listed in Table 1.

5. The probiotic composition according to claim 1, characterized in that it comprises *Bifidobacterium bifidum*, together with at least one of the strains listed in Table 1.

6. The probiotic composition according to any one of claims 1 to 5, characterized in that the said composition additionally includes at least one prebiotic agent.

7. The probiotic composition according to claim 6, characterized in that the said prebiotic includes fucose-containing glycans.

8. The probiotic composition according to claim 6, characterized in that the said prebiotic is lacto-N-biose I.

9. A method of tailoring a probiotic composition based on the spectrum of bifidobacteria found from the intestine of at least one individual with non-secretor blood group phenotype.

10. Use of the secretor/non secretor blood group status of an individual in assessing the need for bifidobacteria-enriched probiotic supplementation.

11. A method of assessing the need of an individual for bifidobacteria enriched probiotic supplementation by determining the secretor/non-secretor blood group status of the individual.

12. A method of assessing the need of a brest-feeded or weaning baby for bifidobacteria enriched probiotic supplementation by determining the

secretor/non secretor blood group status of the baby and that of the baby's mother.

13. A use of the secretor/non secretor blood group status of an individual in estimating a dose of bifidobacteria supplementation needed for a desired effect.

14. A method of identifying an individual at risk for suffering from a gastrointestinal disorder by determining the secretor/non-secretor blood group status of said individual.

15. The probiotic composition according to any one of claims 1 to 5, characterized in that the composition is tailored for infants of the non-secretor type.

16. The probiotic composition according to any one of claims 1 to 5, characterized in that the composition is tailored for infants regardless of their secretor phenotype, whose breast-feeding mother is of the non-secretor blood group type.

17. The probiotic composition according to any one of claims 1 to 5, characterized in that the composition is tailored to elderly individuals for supporting the maintenance of bifidobacteria diversity and abundance.

18. The probiotic composition according to any one of claims 1 to 5, for use in the treatment and/or prevention of inflammatory bowel disease, diarrhoea, respiratory tract infections, irritable bowel syndrome and/or atopy/allergy.

Figure 1

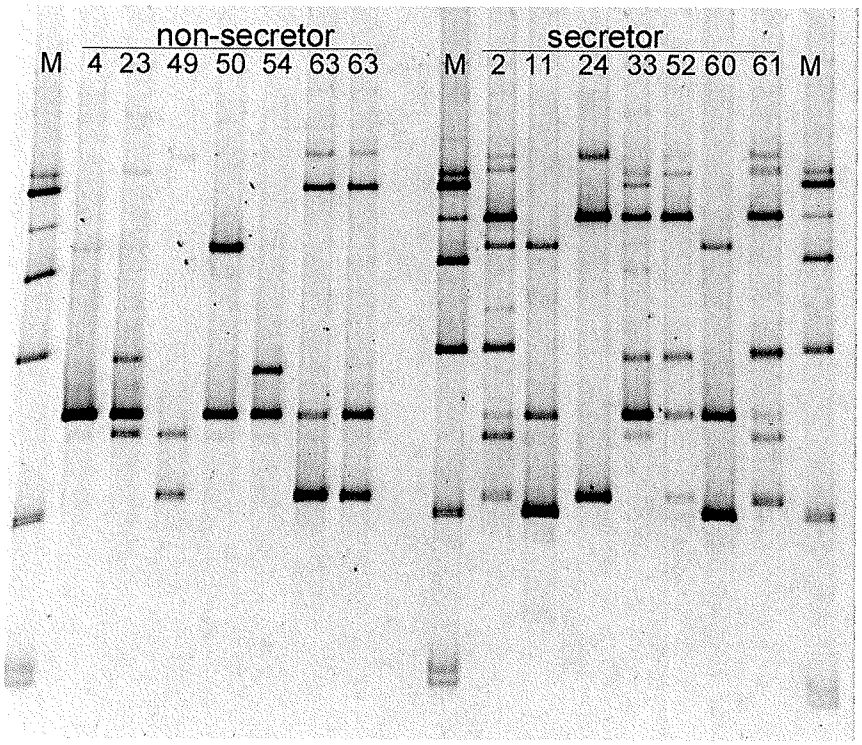
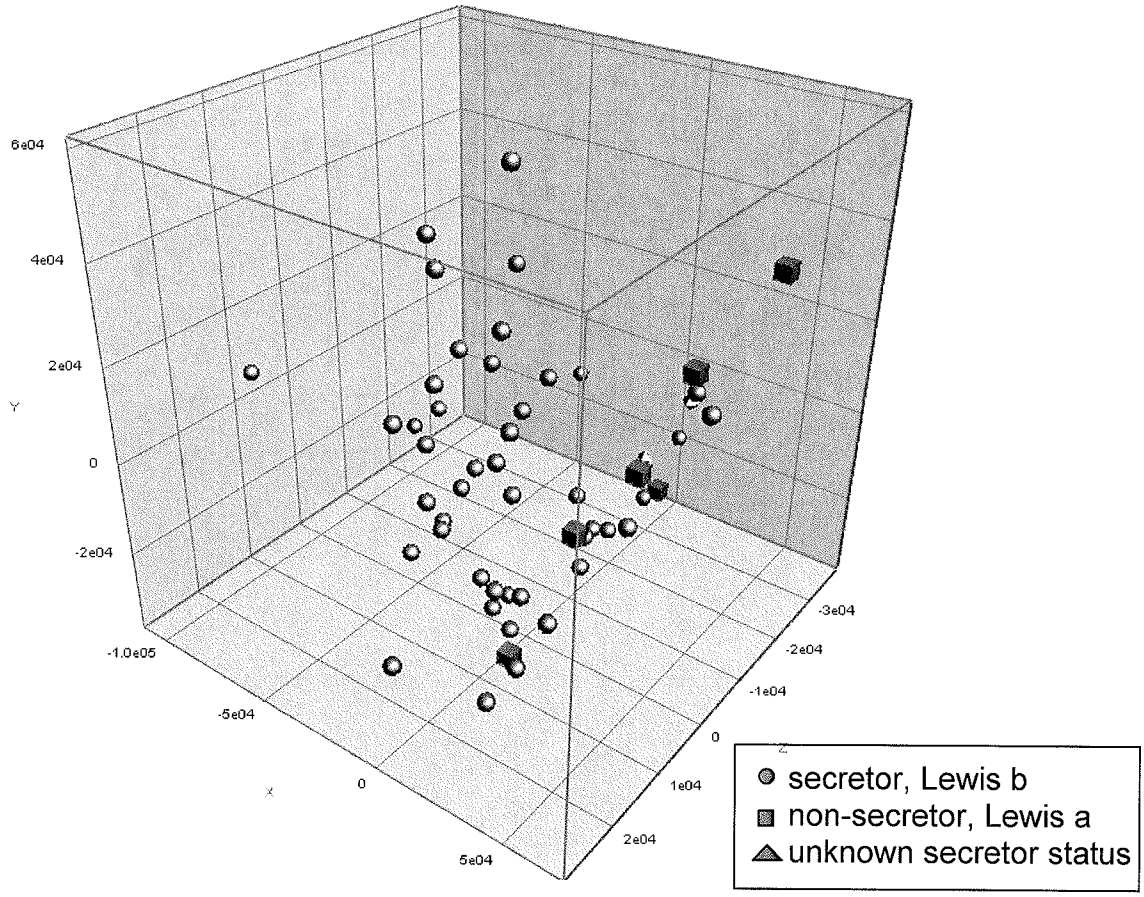


Figure 2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Y
0
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-1.0e05
-5e04
0
X
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2e04
1e04
0
-1e04
-2e04
-3e04
Z
secretor, Lewis b
non-secretor, Lewis a
unknown secretor status

Figure 3

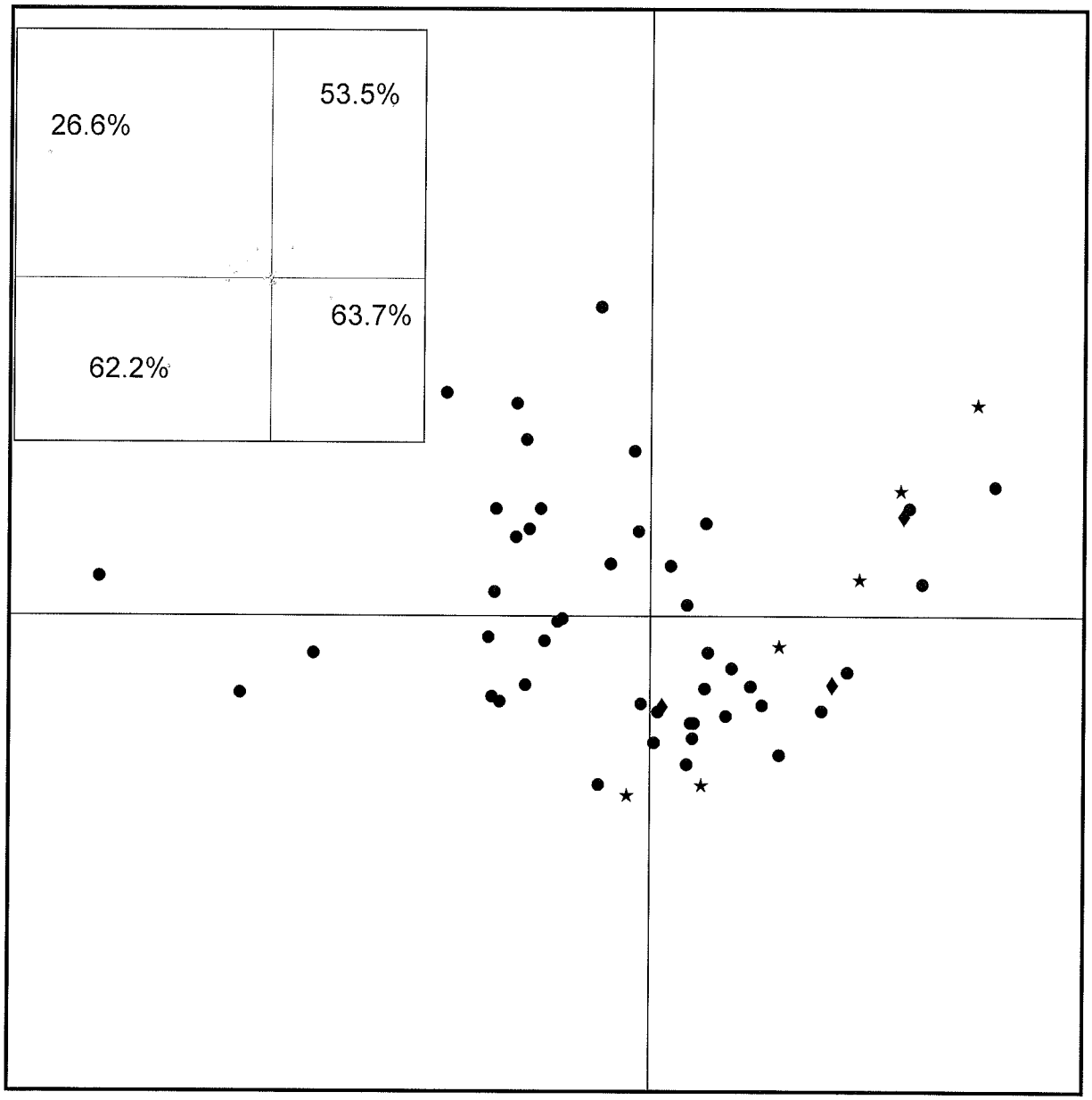


Figure 4

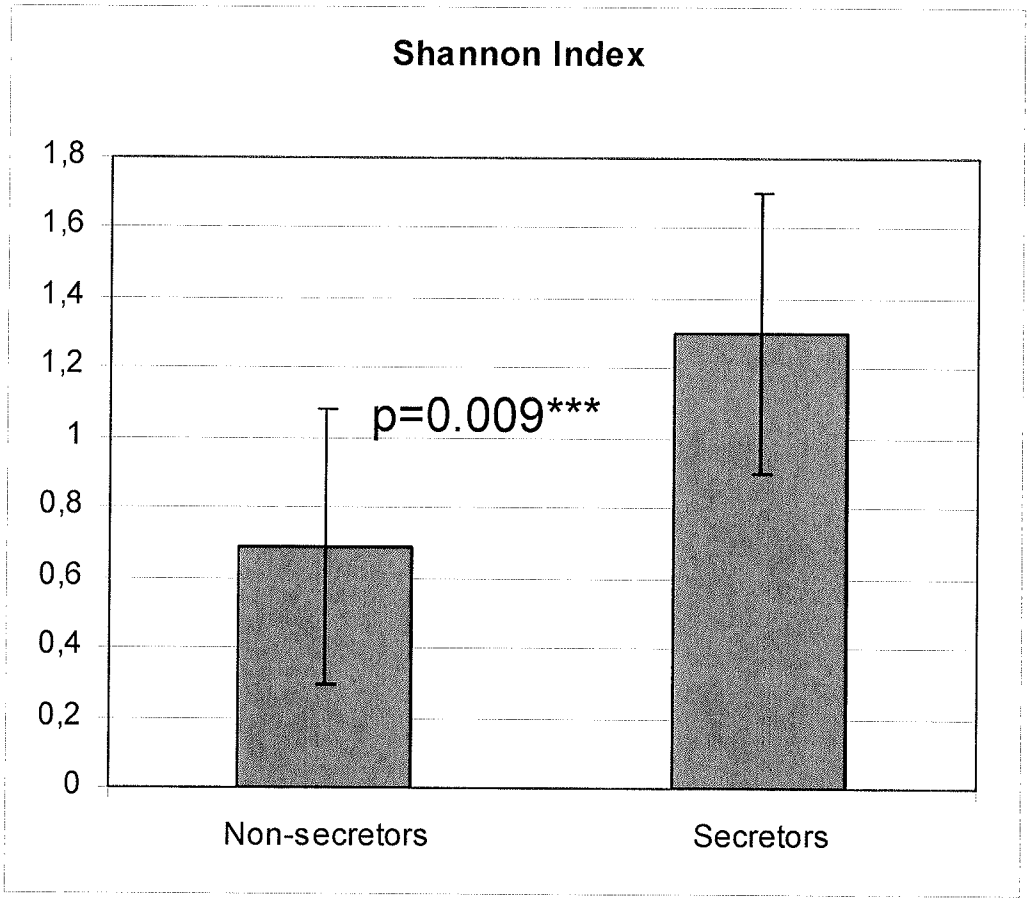

Shannon Index
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
p=0.009***
Non-secretors
Secretors

Figure 5

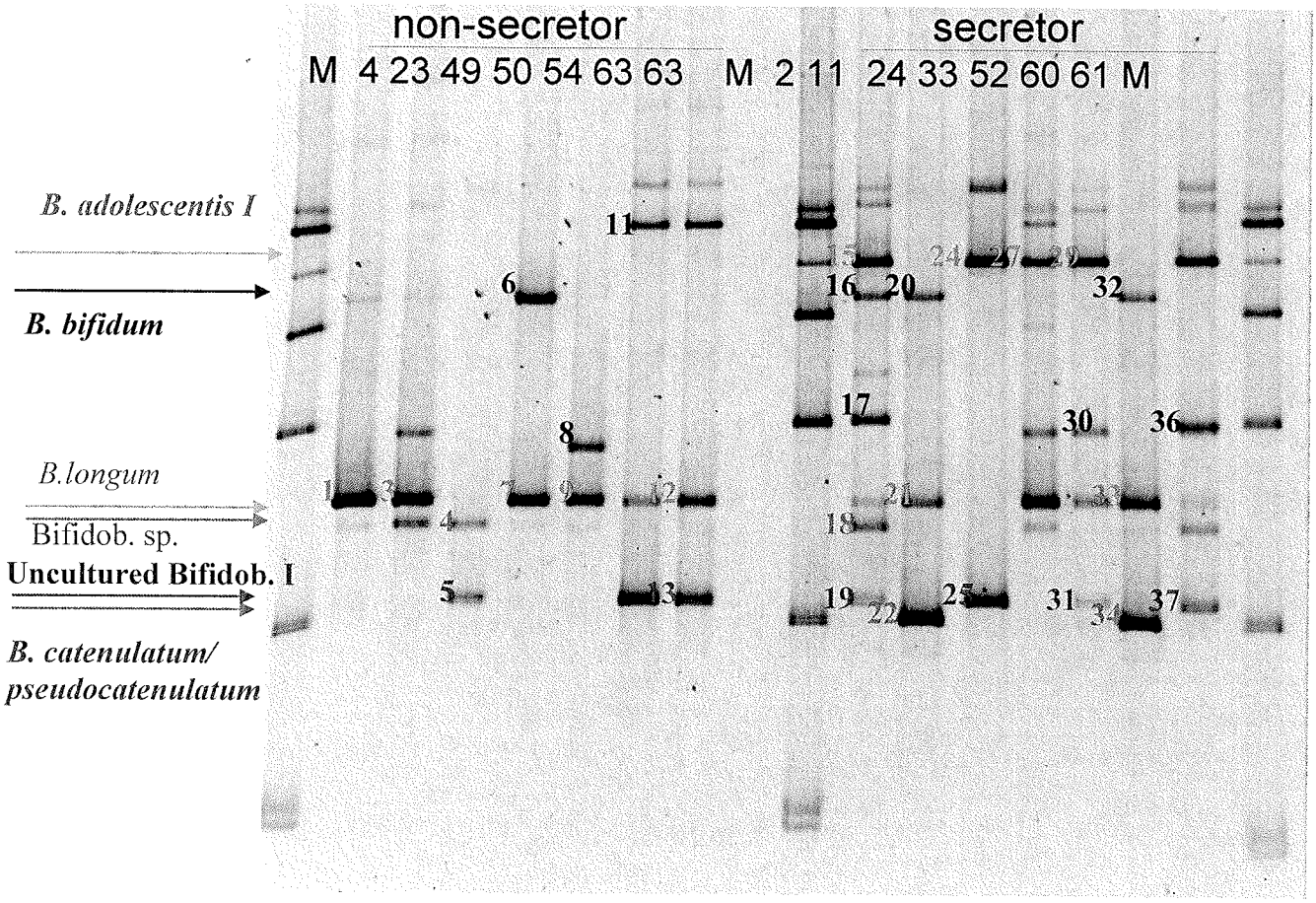
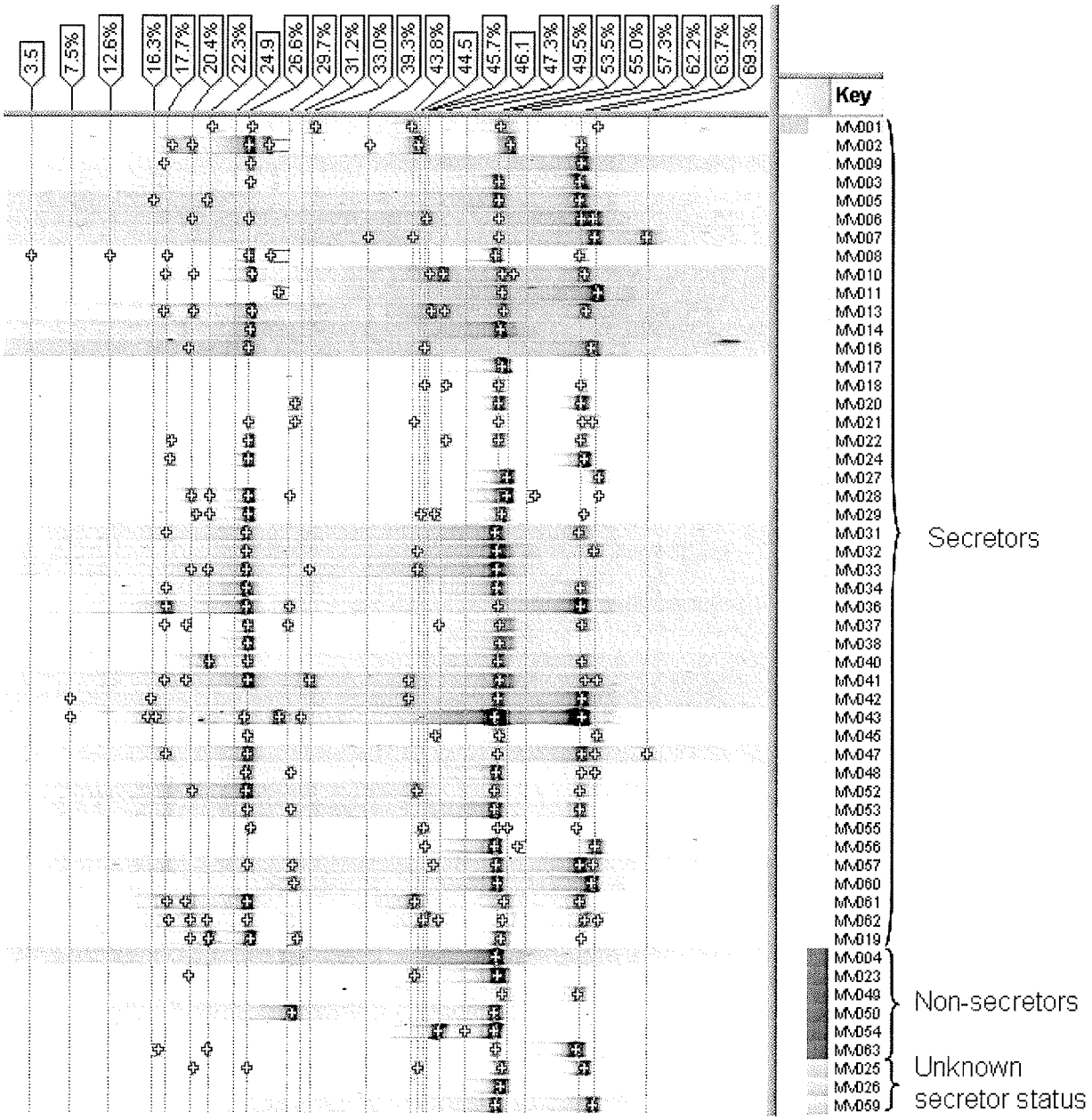

non-secretor
secretor
M 4 23 49 50 54 63 63 M 2 11 24 33 52 60 61 M
B. adolescentis I
B. bifidum
B.longum
Bifidob. sp.
Uncultured Bifidob. I
B. catenulatum/
pseudocatenulatum

Figure 6


3.5
7.5%
12.6%
16.3%
17.7%
20.4%
22.3%
24.9
26.6%
29.7%
31.2%
33.0%
39.3%
43.8%
44.5
45.7%
46.1
47.3%
49.5%
53.5%
55.0%
57.3%
62.2%
63.7%
69.3%
Key
MV001
MV002
MV009
MV003
MV005
MV006
MV007
MV008
MV010
MV011
MV013
MV014
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MV055
MV056
MV057
MV060
MV061
MV062
MV019
MV004
MV023
MV049
MV050
MV054
MV063
MV025
MV026
MV059
Secretors
Non-secretors
Unknown secretor status

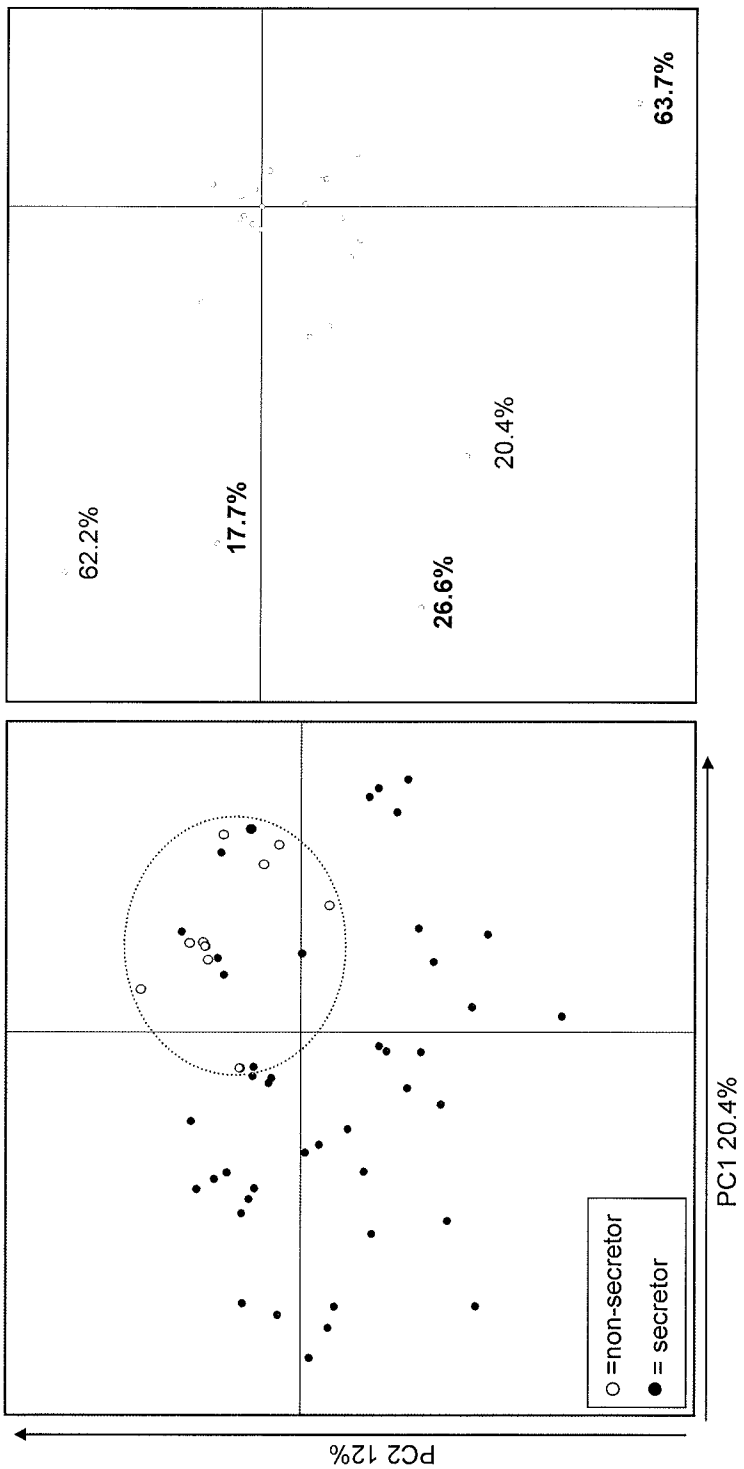
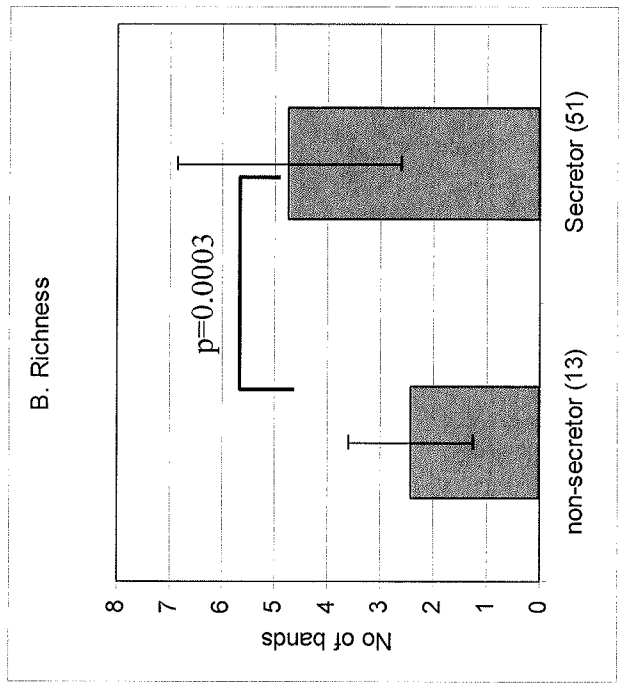


Figure 7


B. Richness
No of bands
0
1
2
3
4
5
6
7
8
p=0.0003
non-secretor (13)
Secretor (51)

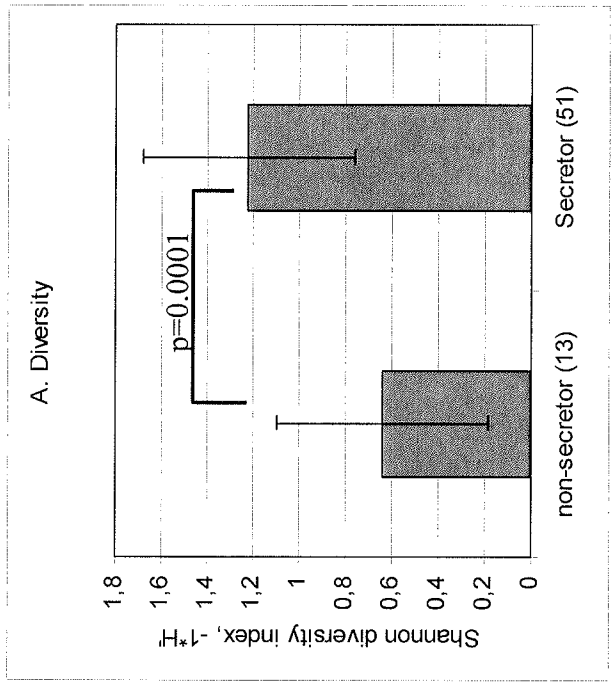

A. Diversity
Shannon diversity index, -1*H'
0
0,2
0,4
0,6
0,8
1
1,2
1,4
1,6
1,8
p=0.0001
non-secretor (13)
Secretor (51)

Figure 8

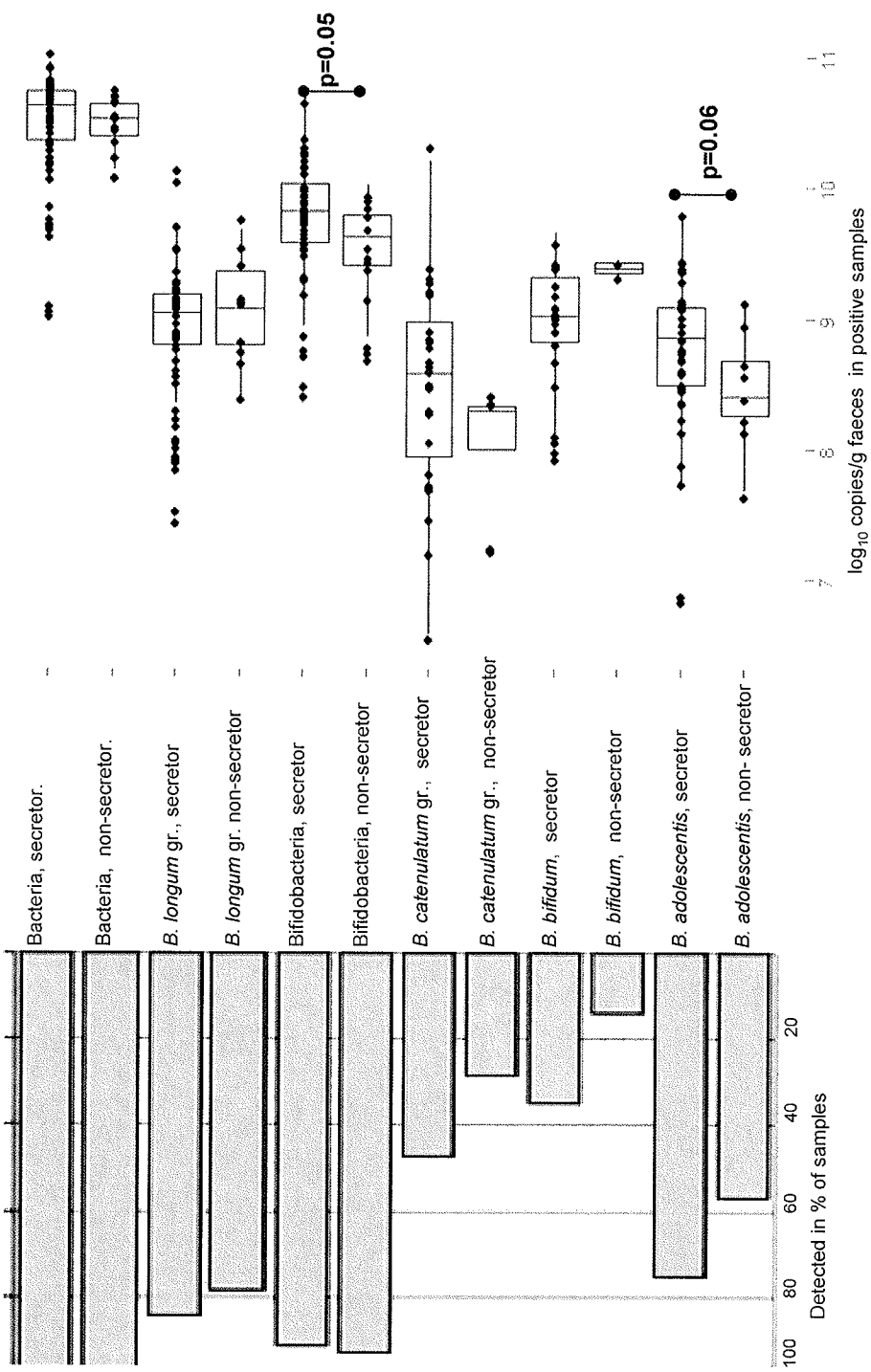

Bacteria, secretor.
Bacteria, non-secretor.
B. longum gr., secretor
B. longum gr. non-secretor
Bifidobacteria, secretor
Bifidobacteria, non-secretor
B. catenulatum gr., secretor
B. catenulatum gr., non-secretor
B. bifidum, secretor
B. bifidum, non-secretor
B. adolescentis, secretor
B. adolescentis, non- secretor
p=0.05
p=0.06
Detected in % of samples
100 80 60 40 20
log10 copies/g faeces in positive samples
7 8 9 10 11

Figure 9