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The genomic basis of the *Streptococcus thermophilus* health-promoting properties

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BACKGROUND

- ✓ *S. thermophilus* is a Gram-positive bacterium used as starter in dairy industry and traditional fermented products
- ✓ Well adapted to the milk environment due to its genomic plasticity and population evolution
- ✓ Used as probiotics for several years with various beneficial effects (alleviation of lactose intolerance, inhibition of pathogens, prevention or treatment of inflammatory gut diseases...)
- ✓ Most of the bacterial factors and mechanisms behind these beneficial effects remain unknown
- ✓ **Aim:** Comparative genomic study of 79 representative strains on bacterial activities known to be beneficial on host physiology

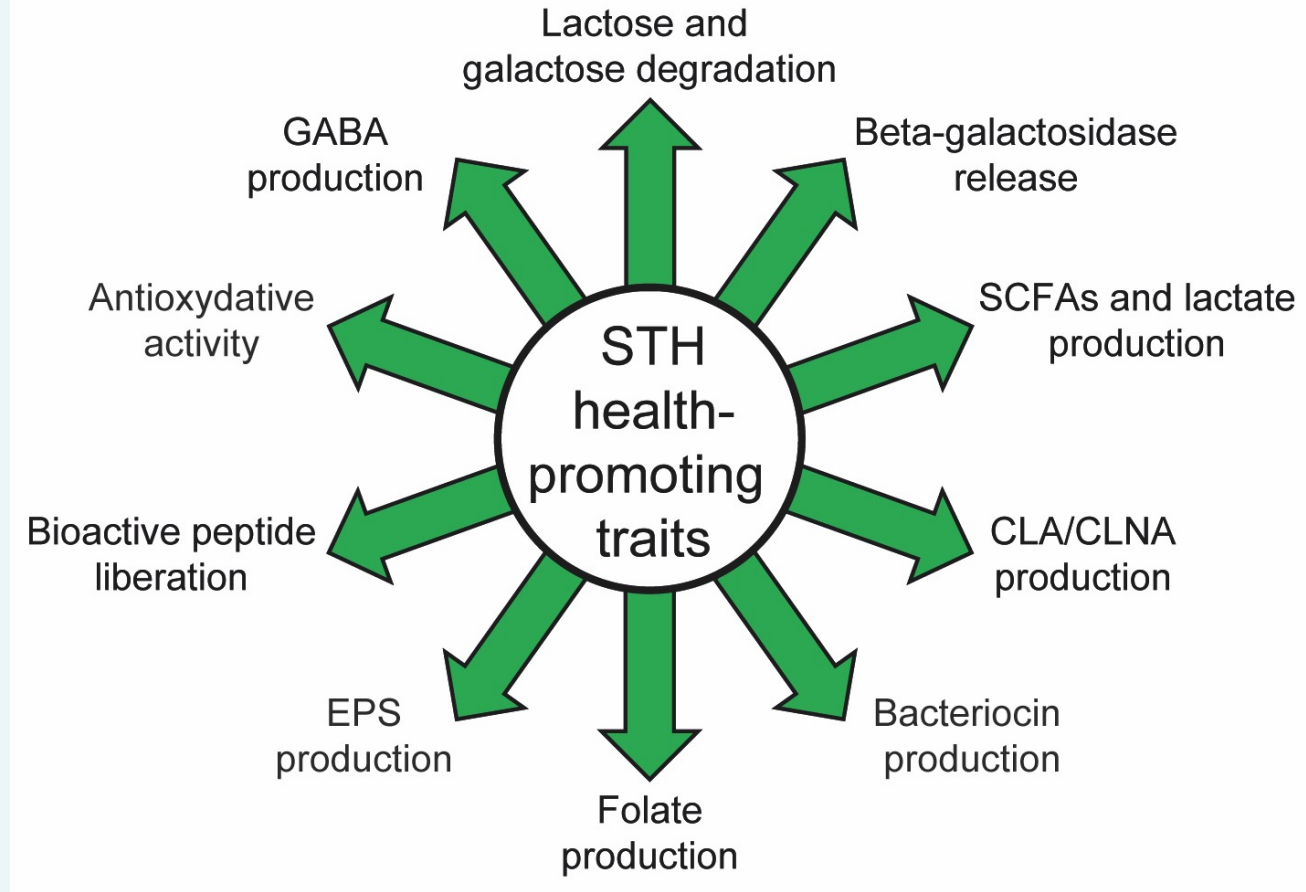


Figure 1: Health-promoting properties of *S. thermophilus*

METHODS

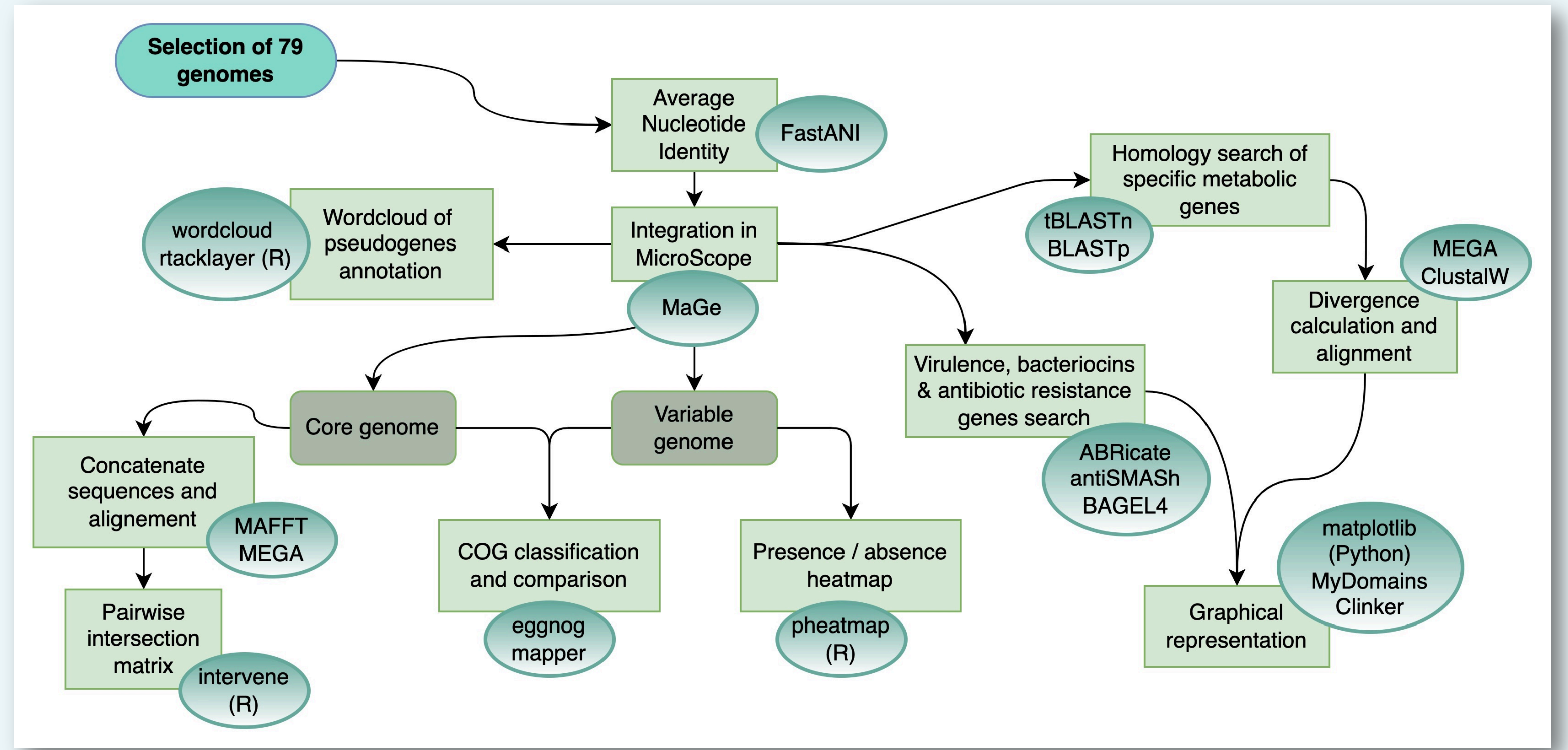


Figure 2: Synthetic workflow analyses

RESULTS

Strain characteristics

- The 79 selected STH strains are :
- ✓ isolated over a long time period (1954 to 2018)
 - ✓ isolated from diverse products (cheese, yogurts, kefir grains...)
 - ✓ isolated in 19 countries

Production of bioactive peptides

- ✓ 19 strains have a complete *prtS* gene
- ✓ Degradation of bovine milk proteins by PrtS liberates bioactive peptides (angiotensin-I-converting enzyme inhibitors, immunomodulators, antioxidants, antibacterials, ...)

Production of GABA

- ✓ 29% of STH strains contain the *gadB* and *gadC* genes coding for the glutamate decarboxylase enzyme involved in the irreversible conversion of glutamate into GABA and the GABA/Glutamate antiporter, respectively.
- ✓ The *gadBC*-containing region tends to undergo multiple evolutionary events and may have been acquired by HGT.

Production of biogenic amines

- ✓ Only a few STH strains (6/79) contains genes coding for histamine production from histidine (the HcdA histidine decarboxylase proenzyme, the HcdP histidine/histamine antiporter, and HcdB, which is involved in HcdA maturation).
- ✓ Concerning tyramine, tryptamine, phenylethylamine and putrescine production, no protein/genomic region with homology to known decarboxylase is detected in the 79 STH genome sequences.

Resistome and Virulome

- ✓ No virulence factors are found.
- ✓ Only two genes potentially conferring resistance to antibiotics were detected in nine strains:
 - ✓ 4 strains encode *mefE*; but *mefE* alone is likely not able to confer high-level macrolide resistance in STH
 - ✓ 5 strains encode *tet(S)* leading to a tetracycline resistance
- the absence of virulence factors and the low occurrence of antibiotic resistance genes contribute to the safety status of the species.

Production of conjugated linoleic and linolenic acids

- ✓ The genome of six strains encodes a protein annotated as linoleate isomerase involved in CLA/CLNA synthesis

Antioxidative activity

- ✓ STH can produce various molecules that decrease the risk of reactive oxygen species such as glutathione, GABA, CLA, folate, EPS, betalactoglobulin-released peptides
- ✓ glutathione peroxidase activity is predicted in 12 strains

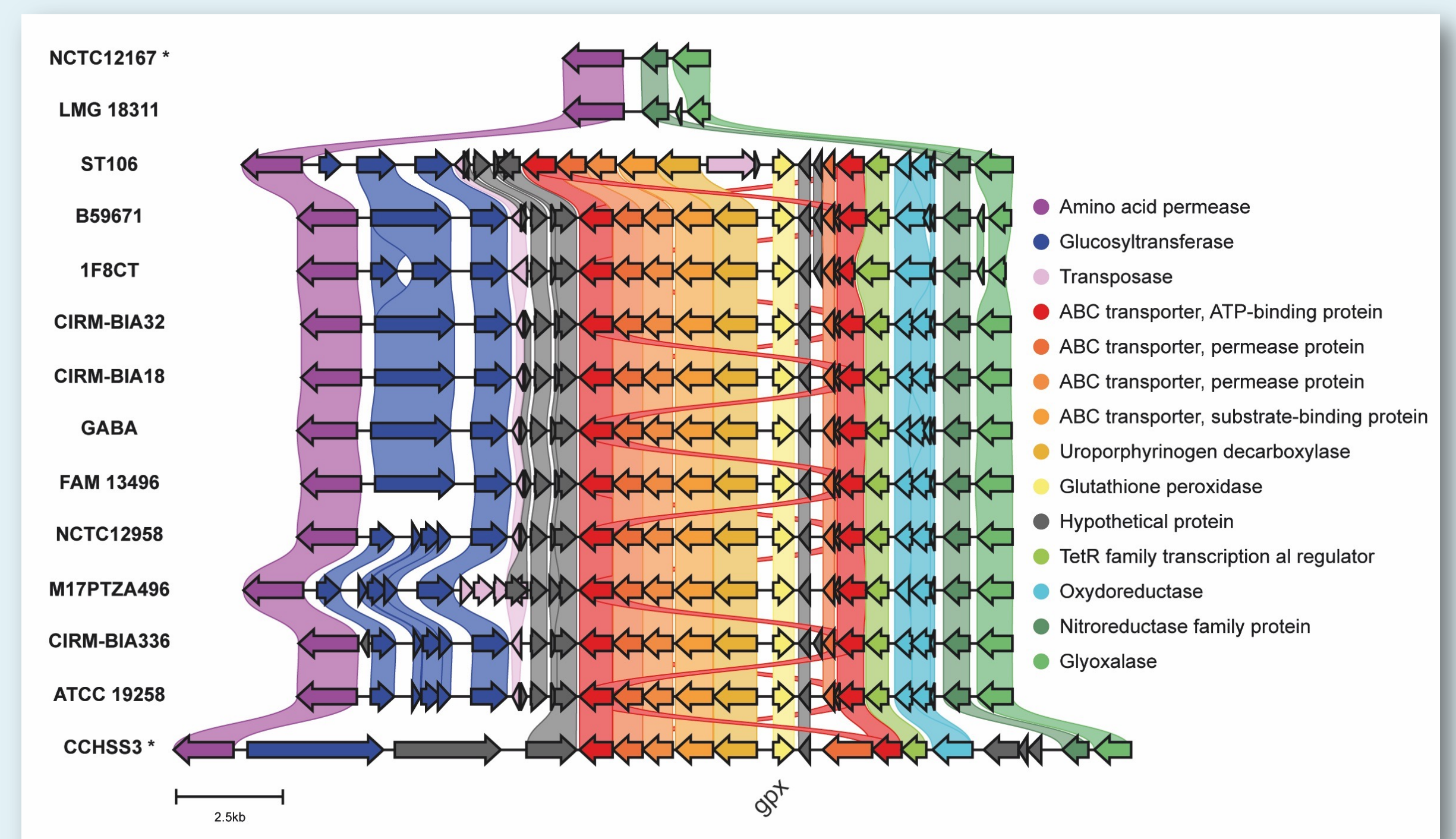


Figure 3: Comparison of the genomic region harboring the *gpx* gene in various *S. thermophilus* strains, *S. vestibularis* NCTC12167 and *S. salivarius* CCHSS3.

Lactose and galactose metabolism

- ✓ 100% of STH strains are Lac+
- ✓ 21% of strains could display Gal+ phenotype:
 - ✓ 15 strains contain the same nucleotide G-to-A substitution in the -10 box of Gal+ mutants
 - ✓ 2 strains contain genes coding for the tagatose-6-phosphate pathway

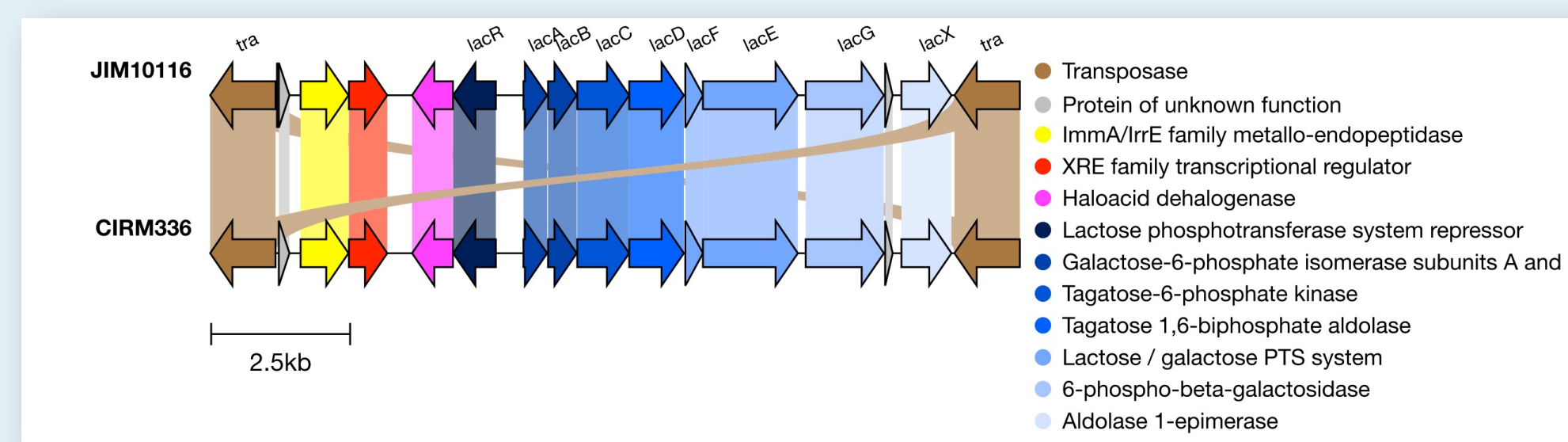


Figure 4: Genetic organization of genes coding for the tagatose 6P pathway in strain JIM10116 and CIRM-BIA336.

Production of bacteriocins

- ✓ STH strains produce bacteriocins with inhibitory activity against Lactic Acid Bacteria, *Listeria monocytogenes*, *Enterococcus faecalis*, *Enterococcus faecium*, *Clostridium botulinum*, *Bacillus cereus*, *Staphylococcus carnosus*, *Salmonella typhimurium*, *Escherichia coli*, ...
- ✓ From one to seven regions of each genome are predicted as coding for bacteriocins: butyrivibriocin, lanthipeptides, streptide and Blp (*blp* locus is ubiquitous in STH strains, except for two strains)
- ✓ Tools for bacteriocin prediction *in silico* are interesting but *in vitro* experiments remain necessary to assess the antimicrobial activity of a strain
- STH species is a promising source of natural antimicrobial peptides with great potential in food biopreservation

CONCLUSION

The results of this comparative genomic study provide a sound basis for future studies on STH. Notably our analysis provides targets for further phenotypic characterizations and experimental validations. While **some beneficial traits are widely shared** among isolates suggesting their **central physiological and ecological role for the species** (e.g., degradation of lactose, folate production), others including the **tagatose-6-phosphate pathway** involved in the catabolism of galactose, and the production of **bioactive peptides** and **GABA** are **highly strain-specific**. Most of strain-specific health-promoting features seems to have been acquired via **horizontal gene transfer events**. The natural intra-species diversity of STH, therefore, represents an interesting source for innovation in the field of fermented products enriched for healthy components that can be exploited to improve human health. A better knowledge of the health-promoting properties and their genomic and genetic diversity within the species may facilitate the selection and application of strains for specific biotechnological and human health-promoting purpose.

