Microbiome studies help explore treatments for genetic disorders

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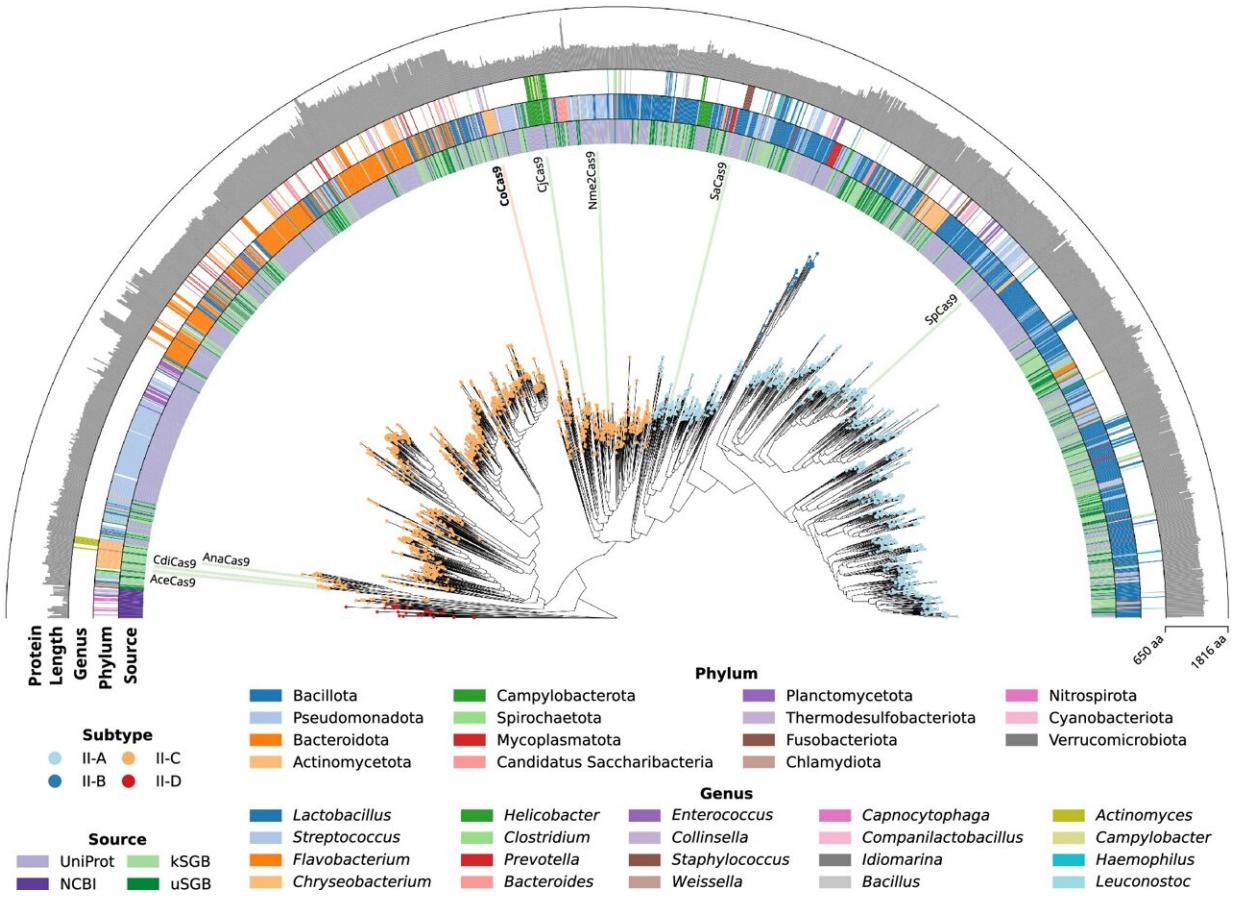

Phylogenetic tree of Cas9 proteins. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-47800-9

A collaboration has led to the identification, in a bacterium of the

intestine, of new CRISPR-Cas9 molecules that could have a clinical potential to treat genetic diseases such as retinitis pigmentosa, through sub-retinal injections. Anna Cereseto and Nicola Segata of the Department of Cellular, Computational and Integrative Biology of the University of Trento have joined forces and combined their expertise to develop new therapies for the treatment of genetic diseases.

A study, with Anna Cereseto and Nicola Segata as corresponding and senior authors, has been published in *Nature Communications*.

Researchers all over the world are investigating genomic therapies to find new treatments for genetic disorders. Genome editing using the CRISPR-Cas9 system is based on the use of the Cas9 protein, which works like a pair of molecular scissors that can be programmed to make specific modifications in the genome to cut or replace harmful DNA sequences, correcting the mutations that cause diseases.

This biotechnology was discovered in 2012 in the United States and has already led to one approved therapy, a drug for sickle cell disease.

Now the study conducted by the University of Trento brings genomic research one step forward.

"Compared with other CRISPR-Cas9 approaches, the one we have identified is precise and effective, and more compact. This new CRISPR-Cas9 molecule, as demonstrated by our experiments in the retina, will be more easily delivered to the organs that must be treated in therapies for genetic diseases," says Anna Cereseto, who has been involved in studies on the genomic editor since 2018 with the development of evoCas9.

Expanding the range of CRISPR-Cas tools is necessary to speed up the development of therapies for genetic diseases. This can be made by modifying natural enzymes, as was the case with evoCas9, but

discovering already evolved enzymes that can work offers great advantages.

The collaboration with the laboratory of Computational Metagenomics of Nicola Segata has allowed the laboratory of Molecular Virology of Anna Cereseto to shed light on a vast natural reserve of CRISPR-Cas9 systems from which to draw new valuable tools for human genome editing.

"By interrogating a microbiome genome database that we have created over several years, we discovered a large number of Cas9 with interesting properties for genome editing," say Anna Cereseto and Nicola Segata.

"We have discovered a great variety of CRISPR-Cas9 in the bacteria that inhabit the intestine. In particular, we have identified the CoCas9 nuclease, a very active group of enzymes with a small molecular size, about a thousand amino acids, in Collinsella, a bacterial genus that is often found in human guts."

"The sequencing of the entire microbiome using a metagenomic approach, followed by the laboratory reconstruction of the assembled genomes, has led to the identification of a huge variety of species. The discovery of a collection of new Cas9 nucleases, including CoCas9, makes the genome editing toolkit even larger," they point out.

They conclude, "The difficulty of administration still hampers the development of therapies for genetic diseases. However, CoCas9, thanks to its small size, shows potential for gene therapy applications and is therefore a potential candidate for optimization through engineering approaches, which deserves further investigation. We are already working on clinical development projects."

More information: Eleonora Pedrazzoli et al, CoCas9 is a compact nuclease from the human microbiome for efficient and precise genome editing, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47800-9

Provided by University of Trento

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