Small genetic differences could spell life-and-death for gut infections

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Drosophila. Credit: Wikipedia

When it comes to fighting gut infections, we are not equal. EPFL scientists have shown how apparently insignificant genetic variation can lead to big differences in the gut's immunity. The study could change the way we treat gut disease.

Consideringhow many microorganisms we ingest each day, our gut has an extensive and well-developed immune system. This defense is involved in acute and chronic gut diseases, but it varies dramatically among people. A persistent question is how our genetic make-up affects our gut's ability to fight infections. EPFL scientists have found that gut immunity is not affected by single genes but by entire groups of genes. The study, which challenges simplistic views of gut disease, is published in *Nature Communications*.

That gut feeling

A healthy gut contains a multitude of beneficial bacteria, which help us digest and process food. But the remaining fifth includes bacteria that can cause infections, which is why the gut has developed an extensive array of defenses. Upon ingestion, bacteria stimulate the gut's cells to produce a mixture of antimicrobial molecules and highly reactive molecules that neutralize infectious microorganisms, but can also damage the gut tissue in the process. In response, cells in the damaged areas release specialized molecules that activate the gut's stem cells to regenerate and heal the tissue.

However, people are not equal in terms of gut immunity. Some individuals are more susceptible to infections than others, even when they share similar diets. For example, two people might eat the same salmonella-ridden hamburgers, but only one of them suffers an infection. The key, therefore, might lie in the genetic variation between individuals. Nonetheless, this is an area of which we still know very little.

Flies to the rescue

The lab of Bart Deplancke, in collaboration with the lab of Bruno Lemaitre at EPFL, have now made a leap forward in advancing our understanding of how genetics influences gut immunocompetence. The researchers showed that we must think beyond single genes and into the far more complex dimension of "gene clusters" - groups of genes working together.

"The problem with genetic variation is, how do you study it in humans?" says Deplancke. "There are so many factors that make it difficult to standardize the comparison e.g. different diets, rates of development, habits during the day and others." Such environmental factors make it difficult to isolate genetic effects.

The team addressed the problem by using fruit flies, which can be easily standardized in terms of environmental factors. This makes it easy to have strains with distinct genetic profiles, while keeping environmental factors the same.

The researchers didn't look at single genes but rather at groups of genes working together. Data from this "genomic" approach would be far more efficient as a starting point in connecting genetics and gut immunity.

PhD student Maroun Bou Sleiman and postdoc Dani Osman infected fruit fly strains with an intestinal bacterium, making sure to keep all other factors, e.g. diet, temperature, humidity - even the amount of infecting bacteria - the same across all strains. The team used over a hundred fruit fly strains with well-defined differences in their sets of genes.

It's all about the genome

What they discovered was that there was a striking variation across the susceptibility of different strains. For example, one strain would show 100% susceptibility to the bacterium (all the flies would die after three days), in another there would be 100% survival, and all others fell somewhere in between (e.g. 50-50 survival etc).

"It has to be the genome," says Deplancke, since all environmental factors such as food, temperature etc. were the same across the strains. "Just having slight differences in the genome can make you anywhere from completely resistant to completely susceptible to an infection."

The question was then finding the biological link between genome variations the gut's ability to fight infections. To answer this, the researchers used two powerful techniques: The first one looked at which genes were "on" in the fly gut; the second one used computers to look at which genetic variants in different fly strains were associated with specific aspects of gut immunocompetence.

The scientists identified several new influencers of gut immunity. These are not single genes, but rather entire groups of genes working together. One group they discovered involved genes linked to the production of the highly reactive molecules that neutralize infectious microorganisms.

This group of genes helps flies resist infections by actually lowering the activity of reactive oxygen species, which minimizes their potential damage to the gut. The group of genes also helps with faster clearance of infectious pathogens and higher stem cell activity for tissue healing. In contrast, this helpful group was less active in susceptible flies, meaning that it could make a life-or-death difference when fighting an infection in the gut.

This study provides completely new insights into what controls the differences in the gut's ability to fight infections, with far-reaching implications that go beyond acute infections. For example, being unable to clear infectious pathogens from the gut or control the gut's immune response, or even to repair damaged tissue after immune responses may lead to chronic gastrointestinal diseases. As Deplancke explains: "Our work shows how relatively minor, but systematic variation in a fly's - and probably a human's - genome can lead to wide differences in the susceptibility of the gut to infections."

More information: Bou Sleiman MS, Osman D, Massouras A, Hoffmann AA, Lemaitre B, Deplancke B. Genetic, molecular and physiological basis of variation in drosophila gut immunocompetence. *Nature Communications* 27 July 2015. DOI: 10.1038/ncomms8829

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