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Study links selection for pathogen-resistance with increased risk for inflammatory disease

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New research reveals that a simple laboratory assay detects a genetic variation in host response to bacterial infection that is associated with an increased susceptibility for inflammatory disease. The study, published by Cell Press online on August 6th in the *American Journal of Human Genetics*, also provides fascinating insight into the link between evolution and the ability to ward off pathogens.

"While previous genome-wide association studies and scans for selection have identified genes important for human disease, there is a growing need for approaches that provide mechanistic information for how variants impact disease pathogenesis and to identify genetic variation in traits subject to natural selection," explains senior study author Dr. Samuel Miller from the University of Washington in Seattle.

Dr. Miller and colleagues used a novel screen of bacterial infection to identify human variation in Salmonella-induced cell death. "By examining variation in human cell-based measures of infectious disease susceptibility and severity, we can begin to link variation affecting human disease and variation identified as being the subject of natural selection," explains lead author Dr. Dennis Ko.

The researchers observed that a more robust host response to Salmonella was associated with nonfunctional CARD8, a gene thought to be a key negative regulator of inflammation. A comparison of CARD8 genes among different mammalian populations suggested that the increase in infectious disease burden associated with animals that live in herds or

colonies may have naturally selected for loss of CARD8 multiple times in mammalian evolution.

A similar process may have occurred in humans, as the authors also showed that loss of function of CARD8 is more common among populations that adopted agriculture earlier, while it is less common in populations that have traditionally lived as hunter-gatherers. The researchers hypothesized that loss of CARD8 may be one way in which a population evolves a more robust host response to deal with infectious diseases.

However, the better ability to ward off infections may be associated with an increased risk for developing inflammatory diseases. Other researchers had already shown a link between CARD8 and severity of rheumatoid arthritis and Dr. Miller and colleagues found in a small clinical study that loss of CARD8 was associated with a modestly increased risk of systemic inflammatory response syndrome, a physiologic state of hyper-inflammation that can have many different causes.

"These results demonstrate the utility of genome-wide cell-based association screens using microbes in identifying naturally selected variants that can impact human health," explains Dr. Miller. "Further, our work provides proof-of-principle that screens for genetic variation associated with infection in humans could be developed to serve as functional tests of susceptibility and outcomes for acute and chronic inflammatory disease."

Source: Cell Press (news : web)