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Study identifies regions of genome associated with cholera susceptibility in Bangladesh

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An international research team has used a novel approach to identify genetic factors that appear to influence susceptibility to cholera. The findings by investigators from Massachusetts General Hospital (MGH), the Broad Institute and the International Center for Diarrhœal Disease Research, Bangladesh (ICDDR,B) indicate the importance of pathways involved in regulating water loss in intestinal cells and of the innate immune system in the body's response to the bacteria that causes cholera, which affects from 3 to 5 million people each year and causes more than 100,000 deaths.

"We sought to understand cholera by studying the genetics of a population that has been affected by the disease for centuries – people in the Ganges River Delta of Bangladesh," says Regina LaRocque, MD, of the MGH division of Infectious Diseases, a co-senior author of the report receiving online publication in *Science Translational Medicine*. "Our findings are just a first step, but they demonstrate how combining ancient history with the current impact of an infectious disease can be a powerful way of identifying human genes that are important to disease outcome."

Cholera is contracted by consuming water or food contaminated with the bacteria *Vibrio cholerae*, which releases a toxic protein upon reaching the small intestine. This toxin binds to the intestinal surface, causing severe diarrhea and potentially death from dehydration. Cholera or a cholera-like illness has been reported in the Ganges Delta for centuries, and most recent global outbreaks of the disease originated in that region. A

potential fingerprint of cholera's genetic impact could be the relative rarity in the region of blood type O, which also confers an increased risk of severe cholera symptoms. The persistence of cholera in the Ganges Delta would be expected to exert an evolutionary force on the population, since individuals with gene variants that reduce their susceptibility to the disease would be more likely to survive and pass those variants along to their children.

To search for genomic regions that affect cholera susceptibility, the team employed a new two-step approach. The first step used a method called Composite of Multiple Signals (CMS) – developed by the Broad team led by co-senior author Pardis Sabeti, MD, DPhil – to scan the genomes of 126 individuals from the Ganges Delta for patterns that signal a long-term increase in the prevalence of particular DNA segments, indicating the effects of natural selection. That scan identified 305 regions under selective pressure, many of which are involved in two important biologic functions: regulation of the passage of water through intestinal cells via structures called potassium channels and a signaling pathway involved in both the innate immune system and the maintenance of the intestinal lining.

The second step directly tested the potential impact of these selected regions on cholera susceptibility by comparing the genomes of 105 cholera patients from the region with those of 167 individuals who did not contract the disease despite being exposed to it in their homes. That comparison found that the genomic region most strongly associated with cholera susceptibility in this population was one that the CMS scan had indicated as being under strong selection pressure. Genes in this region relate to an innate immune signaling pathway. LaRocque's team had previously shown this pathway to be activated by exposure to cholera toxin, and the current study identified the potential involvement of several additional genes in that pathway.

"An exciting feature of this project was the way it brought together the expertise in population genetics and natural selection of our collaborators at the Broad Institute with the leadership in addressing the health problems of the developing world of the ICDDR,B team led by Firdausi Qadri, with whom we have a longstanding collaboration," says LaRocque, an assistant professor of Medicine at Harvard Medical School. "Understanding the basic biology of a disease is fundamental to making clinically relevant advances in treatment. Our laboratory is now working on further studies of the innate immune response to cholera, and we believe this work will be highly relevant to developing improved vaccines."

More information: "Natural Selection in a Bangladeshi Population from the Cholera-Endemic Ganges River Delta," by E.K. Karlsson et al. *Science Translational Medicine*, 2013.

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