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Evolution may have pushed humans toward greater risk for type 1 diabetes

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Gene variants associated with an increased risk for type-1 diabetes and rheumatoid arthritis may confer previously unknown benefits to their human carriers, say researchers at the Stanford University School of Medicine. As a result, the human race may have been evolving in the recent past to be more susceptible, rather than less, to some complex diseases, they conclude.

"At first we were completely shocked because, without insulin treatment, type-1 diabetes will kill you as a child," said Atul Butte, MD, PhD, assistant professor of pediatric cancer biology and a bioinformatics expert. "Everything we've been taught about evolution would indicate that we should be evolving away from developing it. But instead, we've been evolving toward it. Why would we have a genetic variant that predisposes us to a deadly condition?"

The researchers speculate that at least some of the risky changes may protect carriers against certain viruses and bacteria — a trade-off that may have made evolutionary sense in the not-too-distant past when infectious diseases were devastating and largely untreatable. It's not clear, however, whether the beneficial effects arise from the disease-associated mutations themselves, or from neighboring genes that tag along when DNA is divvied up into sperm and eggs.

Butte, who directs the Center for Pediatric Bioinformatics at Lucile Packard Children's Hospital, is the senior author of the research, which will be published Aug. 17 in Public Library of Science *ONE*. Graduate

student Erik Corona is the first author of the study and conducted the analysis.

The idea that disease-causing genes can be beneficial is not new. The most clear-cut case involves a gene variant that, when present in two copies, causes sickle cell anemia, which can result in severe pain, organ damage and death. Although it seems that natural selection would work to eliminate the disorder, the variant remains prevalent in some areas of Africa because people with just a single copy are less susceptible to malaria. Evolutionarily the trade-off is worth it: Far more people are protected from malaria than ever develop sickle cell anemia even in today's environment.

Unlike sickle cell anemia, which is caused by a mutation in just one gene, many complex diseases are associated with several variants — specific locations in the DNA where the nucleotide "letters" vary between individuals. These locations are known as SNPs, for single nucleotide polymorphisms. Some of these SNPs are associated with an increased disease risk, while others protect against developing the disease. When calculating an individual's overall genetic risk, it's necessary to consider the net effect of all of his or her variants.

Corona picked seven well-known conditions to study: type-1 and type-2 diabetes, rheumatoid arthritis, hypertension, Crohn's disease, coronary artery disease and bipolar disorder. Previous genome wide association studies have identified several hundred SNPs associated with each disorder. Corona found that of the top SNPs associated with type-1 diabetes, 80 have been recently increasing in prevalence, meaning that they underwent positive selection. Of these, a surprising 58 are associated with an increased risk of the disorder, while 22 appear protective. Similarly, SNPs associated with an increased risk for rheumatoid arthritis were found to be positively selected. In contrast to type-1 diabetes and rheumatoid arthritis, Corona found that we're

evolving away from a tendency to develop Crohn's disease (that is, more protective SNPs than risky SNPs have been positively selected).

Results for the other three disorders — type-2 diabetes, coronary artery disease and bipolar disorder — showed that protective and risky SNPs were positively selected in about equal proportions. "Now we're starting to see little hints as to why this might be the case," said Butte. For example, a recent study in another lab showed that genetic variations in an antiviral response gene called IFIH1 that improve its ability to protect against enterovirus infection (and the resulting severe, potentially deadly, abdominal distress) also increase a carrier's risk for type-1 diabetes. And scientists who study global disease patterns have long noted that the prevalence of tuberculosis varies inversely with that of rheumatoid arthritis.

"It's possible that, in areas of the world where associated triggers for some of these complex conditions are lacking, carriers would experience only the protective effect against some types of infectious disease," said Butte, who pointed out that the cumulative effect of many SNPs in a person's genome may buffer the effect of any one variant, even if it did raise a person's risk for a particular condition.

Regardless of the reason, some evolutionary tenets still apply. Healthier people are, presumably, more likely to reproduce and pass those same genes — be they protective or risky — to their offspring. When conditions changed because of differences in diet, exposures or location as populations move around the globe, carriers of the risky SNPs began to develop the conditions we struggle with today.

Corona and Butte are now expanding their investigation to include even more SNPs and diseases. They are also looking at the genetic profile of various types of tumors to see if there's evidence for positive evolutionary pressure there as well.

"Even though we've been finding more and more genetic contributions to disease risk," said Butte, "that's not really an appealing answer. There have got to be some other reasons why we have these conditions."

Provided by Stanford University Medical Center