

Scientists think they have an origin story for celiac disease

By Nicholas Staropoli — July 8, 2015

The evolution and spread of genetic disease is fascinating because genetic diseases (spread through inheritance only) really shouldn't exist. They are caused by having alleles (versions of a gene) that are detrimental to health and biological fitness, so they should not remain established in a population.



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Natural selection is survival of the fittest. So while it is possible that a genetic disease like Huntington's disease (a neurodegenerative disorder) could remain -- it generally affects those who possess the allele after reproductive age, so doesn't impact an organism's ability to reproduce and pass on the Huntington's allele -- sickle cell anemia is a bigger mystery because it causes a devastating change in shape and function of red blood cells, and can be fatal in childhood. Conventional wisdom would argue that evolution should have gotten rid of it a long time ago, and yet the alleles still persist in our gene pool. Roughly [300,000 children are born](#) [2] each year with this crippling disorder.

How did this disease and similar ones that are spread only through inheritance become so widespread? The answer may lie in an interesting biological principle called the heterozygote advantage.

This occurs when those members of a population who are a heterozygote (for example, those who inherit a different allele for a gene from mom than from dad, e.g. mom passed on allele for blue

eyes, while dad passed on allele for brown) possess a fitness advantage over members who are a homozygote (those who have inherited the same allele from both parents, e.g. both parents passed on the allele for blue eyes) for a particular trait.

Sickle cell anemia is a classic case of heterozygote advantage, and anyone who has taken a general biology class probably remembers this example. [The disease arises](#) [3] when a person has two mutated copies of the hemoglobin gene. When a person is a heterozygote for the hemoglobin gene they have added protection from malaria. In other words, having one healthy copy of the hemoglobin gene and one diseased copy provides a fitness advantage over people who are homozygous for the normal hemoglobin gene (i.e. they inherit two healthy copies).

But there is a trade off. A person who is a carrier (i.e. heterozygote) of the mutated hemoglobin allele has protection from malaria. But if the person they reproduce with is also a carrier they risk having children that have sickle cell anemia.

There are other examples. Being a [cystic fibrosis carrier has been linked with](#) [4] protection from Cholera and Tuberculosis. People who are [carriers for a very common form](#) [5] of deafness have better protection from infection through having a thicker epidermis and have more efficient cell repair machinery.

And it is not just in human evolution. [An allele in sheep](#) [6] that leads to rams with decreased fertility and produces smaller horns has persisted because those rams that are heterozygous for this gene live longer than those who are homozygous for regular sized horns.

The growing list of genetic diseases and disorders that are associated with the heterozygote advantage has led many researchers to search for previously-undiscovered connections. This may offer an explanation for why celiac disease appears to be more prevalent today than in years past.

Dr. Bana Jabri director of research at the University of Chicago Celiac Disease Center, and population geneticist Luis B. Barreiro [hypothesize that celiac prevalence is tied with increased immune activity](#) [7] that historically could have been a fitness advantage. Both scientists argue that as population density increased due to farming and livestock domestication, human life became filthy and having a more active immune system was a fitness advantage as the body tried to fight off a new litany of infectious particles.

Again, there is a tradeoff: an immune system that overreacts to otherwise innocuous substances like gluten.

Celiac does appear to have a genetic basis, and with the ubiquity of wheat in most diets there could be some advantage afforded to those carrying these alleles. Indeed some evidence suggests that these celiac-associated alleles are increasing in frequency, and [40 percent of all Americans](#) [8] are carriers for one of the two most common alleles associated with celiac disease (named HLA-DQ2 or HLA-DQ2).

However, the case might be not as strong as these researchers believe because these celiac-associated alleles behave very differently than those that cause cystic fibrosis and sickle cell anemia.

In [cystic fibrosis](#) [9], if you have the alleles for cystic fibrosis you have the disease. This might sound obvious, but not all alleles work this way. For example, the BRCA genes for breast cancer only lead to breast cancer between 65-80 percent of the time. In biology this is called [penetrance](#) [10], its the odds that having the genes leads to having the associated trait. Penetrance for cystic fibrosis is very high close to 100 percent.

For the HLA-DQ2 or HLA-DQ2 alleles, the penetrance is very low. Consider that 40 percent of Americans carry one of these two alleles yet only one percent of Americans are actually diagnosed with celiac disease. This puts the penetrance of these two alleles at less than one percent. Furthermore, [evidence](#) [11] implicates at least 40 genes in celiac disease. It is a stretch to say that all of these genes are involved in some sort of fitness or adaptive advantage gone awry.

The question of the origin of celiacs disease is a good one. It may tell an interesting evolutionary story, and give us clues on how to treat it. But it s too much to conflate celiac disease with that of sickle cell anemia, which has very demonstrable pathology as well as a demonstrable fitness advantage.

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[3] <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499995/>

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[9] <http://www.alrc.gov.au/publications/2-genetics-and-human-health-primer/importance-penetrance>

[10] <http://www.geneticseducation.nhs.uk/genetic-glossary/221-penetrance>

[11] <http://emedicine.medscape.com/article/1790189-overview>