# Do ‘genetic superheroes’ exist? Or did media overhype Resilience Project?

*Genetic Superheroes. Hitting the genetic lottery. 13 Incredibly lucky people. Bulletproof genomes.*

That’s just a few of the ways people have described the results from a recent analysis of the genomes of over half a million people which found that 13 lucky people have disease causing mutations, but don’t exhibit any symptoms.

The study is the largest effort, to date, to identify so called ‘resilient’ individuals. These are healthy people who possess a mutation in their genome that is known to be disease causing. Many believe the DNA of these resilient people hold the key to treating genetic diseases, like cystic fibrosis, that today are incurable.

The existence of these 13 genetic Herculeses has created much excitement in the media:

- STAT*: Genetic ‘unicorns’ defy their own DNA — and hint at treatments*
- NPR*: How Do ‘Genetic Superheroes’ Overcome Their Bad DNA?*
- BBC: *‘Superhero DNA’ Keeps Diseases at Bay*

But did the study really identify a few lucky winners of the genome lottery? What’s the real story here?

The study published in the journal *Nature Biotechnology* by a team of international scientists led by researchers at Icahn School of Medicine at Mount Sinai in New York City searched the genomes of 589,306 people—all over the age of 30—for 874 genes that are linked to 584 genetic diseases. All of these diseases begin to affect a person during childhood, like cystic fibrosis, Tay-sachs and Pfeiffer syndrome.

The team obtained these sequences from a variety of previous studies, but most of the data—nearly 400,000 samples—came from the at-home, personal genetics test 23andMe. (On the 23andMe consent forms, customers can select a box to allow their DNA to be used in such research.) Pooling all of this data, the scientists identified 15,597 potentially resilient individuals, but after a rigorous screen of these candidates, they eliminated almost all of them, settling on just 13, they believed were resilient.

The study is considered, by the Resilience Project leaders to be a ‘proof of concept’ study which means they modestly set out to prove their methods could identify resilient individuals. The study’s leader, Stephen Friend, says the idea to look for resilient people came out of frustration from the lack of success he had in looking at the problem from the other way. He and other biotech researchers usually search for genetic variants common in a number of sick individuals and then look for ways to fix the defect, but Friend admits they have been largely unsuccessful using this approach. He hopes that by looking for resilient people instead, he will discover why they are resilient and then use that knowledge to treat those who do exhibit symptoms.

But some have begun to question the validity of the resilience of these candidates, which could blow a hole in the conclusions. The study was a retrospective analysis, meaning the authors looked over data from other studies to establish connections, but they did not personally examine any of the participants.

More importantly, for many they *never* can. In several of the studies they borrowed data from, recontact was not even considered when asking for participant consent. For participant's samples from 23andMe, the consent for recontact falls into a gray area because the company does not specifically ask for permission to recontact on its consent form.

*Nature Biotechnology* published an independent commentary from Daniel MacArthur, a geneticist who teaches at Harvard University and conducts research at Massachusetts General Hospital. MacArthur explains why this data collection flaw hurts the study's validity:

> *Perhaps most unfortunately, the researchers could not recontact the majority of resilient individuals for further study because of a lack of necessary consent forms. This means that some of their resilient cases may be mirages (the result of undisclosed disease cases, sample swaps, or somatic mosaicism), and this lack of consent precluded the collection of further clinical and genetic data to explore possible resilience mechanisms.*

Without follow ups, the researchers couldn't confirm if these people are actually as healthy as their medical records suggest. Making matters worse is that some records were obtained from notoriously unreliable self-reports. Further, it's also possible that in the time since their records and DNA were sequenced, their disease status (i.e. diagnosed with the disease) could have changed or they could be exhibiting vague or weakened symptoms that have not been labeled as a specific disease.

Ada Hamosh, the clinical director of McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins University, who was not involved in the study, explained how this could have happened in the study to GLP sister site Genetic Expert News Service (GENeS):

> *The individual carrying the FGFR1 mutation for Pfeiffer syndrome may be a mosaic (i.e. the mutation is present only in certain cell types) or may simply have a mild form of the condition that was not recognized. This is not uncommon for Pfeiffer syndrome.*

Scott Hebbring from the Marshfield Clinic Research Foundation at the University of Wisconsin – Madison, also commenting to GENeS, expanded on Hamosh's point:

> *…In reality, most diseases can be expressed very differently between individuals, even in those who have the same genetic variant. Different environmental exposures and other genetic factors may influence how a genetic variant affects a spectrum of disease outcomes. This study is unique in attempting to assess one extreme in that spectrum. It may not be surprising that some individuals may actually have symptoms but they are either not reported or initially attributed to the genetic variant(s).*

Another problem is that some variants and diseases are so well characterized by scientists that they directly challenge the existence of these resilient individuals. Hamosh believes this is the case for those that appear to be resilient to cystic fibrosis where she believes this finding likely arose from

technical error. Without recontact, the researchers will never be able to explain away these alternate interpretations of their data.

**Can resilient individuals even exist?**

Even if the explanations put forth above explain away the apparent resilience of these 13 individuals, it doesn't mean resilient individuals don't exist in the population. Ada Hamosh was quite critical of the study in her comments to GENeS, but does recognize that resilience to genetic disease does exist and points out that resilience to sickle cell anemia has been previously recorded. But if we do find them, there is reason to believe their DNA may not provide anything of therapeutic value.

This search of genomes for resilient individuals is reminiscent of the controversial genome-wide association studies (GWAS), which are studies of large, diverse groups of people that seek to find commonalities in their DNA that may explain a disease or a condition. Scientists cast a big net over our genomes and hope to draw conclusions based on associations and statistical links between a gene variant and some condition like cancer or heart disease. It is in a sense a genetic fishing expedition.

GWAS have been somewhat successful in identifying a few important connections between traits and gene variants. Yet many of these variants do not tell the whole genetic story, and most have only identified minute increases in risk for disease—on the order of a few percent—partly because there are so many factors that determine overall disease risk. All too often one gene variant cannot explain all of a person's risk, and in many cases, genetics cannot provide the whole explanation on its own. As Hebbring notes, "this study emphasizes, like many preceding disease specific studies, that genetic data is often very important but not always absolute when predicting outcomes." From what we've learned from GWAS, it is easy to see how the search for resilient people could turn up many genetic factors that merely each push the needle towards resilience a small amount.

Despite its doubters, the Resilience Project will go on, as it should. Friend says their next step is a study with 100,000 participants who all agree to being recontacted if their genes reveal they are resilient. When they do publish their next round of results, the media will undoubtedly cover it, but let's hope when they do they leave the 'unicorns' and 'superhero' metaphors behind and focus on the science.

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