

# From Past to Future: Genomics, Evolution, and Aging

## INTERVIEW WITH: DR. PETER SUDMANT

BY: CATHERINE TRAN, ANA SOFIA BRITO, CALI BOND, and TANYA SANGHAL

*Dr. Peter Sudmant is an Assistant Professor of Integrative Biology at UC Berkeley. He earned his PhD in Genetics at the University of Washington before completing a postdoctoral fellowship at MIT in the Christopher Burge Lab. Dr. Sudmant is now an enthusiastic educator and mentor, teaching undergraduate and graduate courses in biology and genomics here at UC Berkeley. His research discusses the genetic and evolutionary mechanisms underlying diversity and adaptation in both humans and other species. Working alongside his team in the Sudmant Lab, he specializes in understanding how genetic variation shapes phenotypic outcomes. His research incorporates multiple fields, including comparative genomics, computational biology, and molecular impacts of structural genetic variation and aging.*



Dr. Peter Sudmant

**BSJ:** What inspired your interest in genomics and the study of aging?

**PS:** I thought it was really interesting—thinking about human disease. Almost all common human diseases have age as a primary risk factor. Cancers, Alzheimer's, dementia, heart disease, diabetes, for example, all have age as a primary risk factor. Then, I was also really interested in biodiversity. On this planet, there is a 150,000 fold variation in lifespan organisms on this planet. It is really interesting to think about how, in our own species, there are all these diseases where age is playing a very important role. But age is also this very plastic thing in the natural world, where there are all these different life spans.

**BSJ:** Adding on to that, what is the importance of genomics research in modern society?

**PS:** Genomics is the extension of genetics, which is an extension of biology. Biology is the study of diversity, and genetics is the study of heritability. What we have learned about genomics is basically using state of the art technologies and sequencing technologies to understand the processes of heritability. I see genomics as basically a tech-driven approach to studying genetics. And I see genetics as the core of biology because it is how we understand both evolution and evolutionary processes as well as heritability.

**BSJ:** Could you highlight some of the differences between the different amylase genes: amylase 1 (AMY1) amylase 2A

(AMY2A), and amylase 2B (AMY2B). Why do we see variations among different populations?

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**PS:** AMY1 is expressed in the saliva, so if you take a piece of pasta and put it in your mouth, eventually it will get a little bit sweet. That is your salivary amylase breaking the starches down into sugars. That is where that particular gene is doing the most work. The other two amylase, AMY2A and AMY2B are expressed exclusively in the pancreas, creating enzymes that are working in your gut to digest starches. So, they are playing two distinct roles there. The question of why we see diversity is in some ways perhaps unresolved. But what we believe has happened is that maybe half a million years ago (300,000 - 500,000), there was a duplication. All great apes, such as chimpanzees, have all three of these copies, AMY1, AMY2A, and AMY2B. We estimate that about 300 to 500,000 years ago, there was a duplication event that created three copies of AMY1 and left those single copies

of AMY1, AMY2A, and AMY2B. The way the mutational processes work is that once there are more copies, you are more likely to get more structures created. This happens through a process called non-allelic homologous recombination. There has been a lot of diversity created through these mutation processes. We think that when humans started eating more starches whether in different contexts, through during the agricultural revolution, or even earlier during the gathering stage perhaps previous to that from having access to certain kinds of things that they were gathering throughout the world, then there was selection on that variation that existed, which provided some fitness advantage.

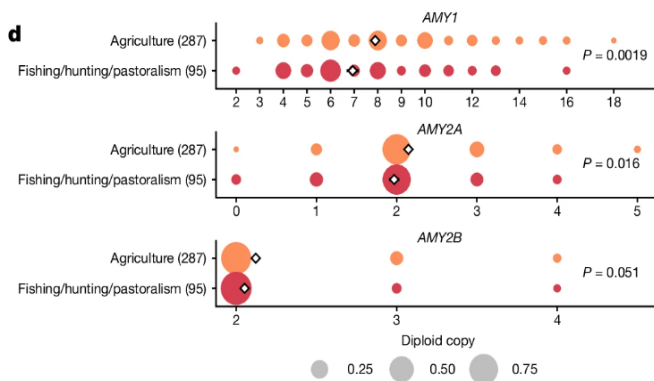
**BSJ:** In your research, you had mentioned a little bit about evolutionary trade-offs. Could you explain a little bit more what that evolutionary trade off that the increased level of amylase has led to, and what could be done about the consequences of amylase breakdown of carbohydrates?

**PS:** We don't know that there's a trade off, but one hypothesis is that the ability to better digest amylase comes at the cost of their basics, especially the cellular amylase, which would be more sugar in your mouth and hidden cavities. There could be many more reasons why there are trade offs, but that seems to be one potential trade off. The trade off being that while you get more nutrition from starches with increased copy number, you also get more cavities.

**BSJ:** Do you think the emergence of multiple amylase genes is related to the shift of hunter gatherers to agricultural based societies? What can you say about this lifestyle shift?

**PS:** Our species started eating a lot more plant matter and starch derived material when we transitioned from hunter gatherer to farming sedentary lifestyles. One hypothesis is that these populations have experienced positive selection to favor people with higher copies of amylase. We provide some evidence of that, potentially in Europeans, in our study, though it's still something of an open question. And today, people who have extremely carbohydrate rich diets are nowhere near hunter gatherer based diets and so across the world, one would hypothesize that over the last 12,000 years or so, there's been positive selection, but it is hard to say precisely.

**BSJ:** Your research mentions that populations with higher amounts of amylase genes are adapted to starch digestion,



**Figure 1: Amylase copy number diversity.** The copy number distributions of AMY1 (top), AMY2A (middle) and AMY2B (bottom) in 33 modern human populations with fishing-based, hunting-based and pastoralism-based diets.

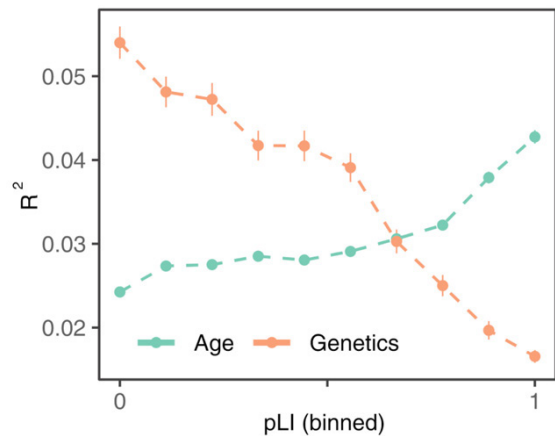
noting the rise of obesity and metabolic disorders in the US specifically. Do you think that genetic differences in these genes have evolved in response to differences in our modern diets?

**PS:** I do not think that there has been selection for our modern lifestyles yet, and while other people have looked, there has been no conclusive evidence linking amylase copy number and obesity. The reason why there have been conflicting results is because it is such a complex region to look at. Some of the work that we have done recently, makes this region easier to look at. We are in a better place to address that question for the first time, to actually go back and re-look at that question.

There are a bunch of nested questions here making it hard to answer: we find evidence that a higher copy of amylase was potentially adaptive to the emergence of for the starch-rich diets that we started eating during the agricultural revolution. Our modern diets are very different from those of our 12,000 or even 100 years ago. Modern diets do predispose to metabolic disorders. We have no evidence that amylase gene copy is associated with metabolic disorders.

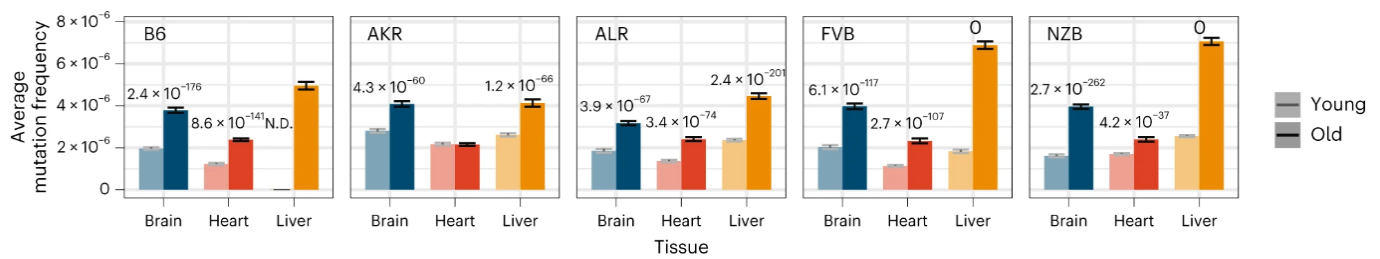
**BSJ:** Turning to another research interest of yours, could you give us an overview on selectivity and malfunction of genetic expression as human ages increase?

**PS:** One question that we like to think about in our lab is: as we age, what happens to the molecular processes in our cells? How are they changing? There are different contributions to those molecular processes—one of those contributions is the contribution of genetics. So how much are your alleles from your mom and dad contributing to what is going on in the individual cell, and how much is your age impacting that? We have done some work trying to look at gene expression and how much of the expression can be attributed to your genetics versus your age. What we found is that there is actually a fair amount of contribution of age to your gene expression, and the types of genes that are associated with your age are very different kinds of genes that are associated with your genetics.



**Figure 2: Evolutionary signatures of aging.** Gene expression variance shown by genetics or age as a function of binned (10bins) gene constraint averaged across all tissues.

**BSJ:** Given the observation of age related declines in mitochondrial and translation gene expression across multiple tissues, what does this mean about broader implications of age related processes, and how might this influence the future of aging research?



**Figure 3: Region-specific changes in somatic mutation frequency with age.** The average mutation frequency for young (light) and aged (dark) mice in each experimental condition is shown. Specific tissues examined were the brain, heart, and liver. Mutation frequency was calculated by dividing the total count of alternative alleles by the duplex read depth at the position along the genome.

**PS:** We are doing very basic aging research, and identifying a lot of different molecular correlates of aging research. I think the big picture is that we are learning more about the molecular processes that are going on, but a lot more work is needed in the immediate future—the most important sources of interventions are likely to be social and economical things, like diet, exercise, access to health care. In the long term, we hope that by understanding all the different molecular processes ongoing, we can better understand why so many diseases have age as the primary risk factors.

**BSJ:** You have a study that reveals that certain tissues, like the prostate and lung, defy Medawar’s hypothesis and do not follow the typical aging pattern where genetic control becomes less strict over time. Why do you think these specific tissues remain so tightly regulated as people age, and could this suggest an adaptive advantage in aging populations?

**PS:** The Medawar’s hypothesis proposes that is basically that genes that are expressed earlier in life should be under increased constraint compared to those late in life because they are important for the survival of a species. It turns out that, at the level of gene expression, that is very much true for the most part—genes that are expressed very early in life are much more conserved than genes that are expressed later in life. Conserved means that there is an evolutionary signature that deleterious mutations are being rejected in the population or through evolutionary time. There is a class of tissues, which we termed “non-Medawarian” tissues, which actually showed the opposite pattern: genes that were expressed later in life were more constrained than the genes that were expressed earlier in life. We are not sure why. One of the things we noticed is that those tissues tend to be highly proliferative, i.e. turning over very, very quickly. The reason why those so-called non-Medawarian tissues look non-Medawarian is that all these really important developmental pathways for gene division and replication are being turned on later in life because we need to keep replenishing the old cells of your lungs, for instance. But there is the double edged sword that because those tissues need to be continuously proliferating throughout their lifespan, they are going to be more sensitive to getting cancers, cancer-causing mutations, etc.

**BSJ:** What could the next steps be in approaching the problematic impact of aging on gene expression?

**PS:** That question is sort of unresolved. Is it cause or effect? Do we know exactly why these genes are changing their expression with aging? Is aging causing it, or is that your genes themselves

changing causing aging? TAnd the kind of research we are doing is very basic science, so we are not necessarily linking it directly to human health outcomes overall. That said, one thing to think about is as you get to bigger and bigger cohorts of people who are start studying these kinds of questions, we can start looking at our study as very generic, just looking solely at aging. We can start looking at the true health outcomes of people. Once we can start linking those things, then we can maybe start begin generating hypotheses about what things we might want to tweak to make sure that people have healthier lives and long health spans.

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## IMAGE REFERENCES

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