PLOS Science Wednesday: Hi reddit, my name is Rebekah Rogers and I found that, before extinction, two different species of woolly mammoths had bad genetic mutations, which likely didn't help their survival – Ask Me Anything!

PLOSScienceWednesday [1] and r/Science AMAs[1]

[1]Affiliation not available

April 17, 2023

Abstract

Hi Reddit, My name is Rebekah L. Rogers and I am an Assistant Professor in the Department of Bioinformatics at UNC Charlotte. My research focuses on genome structure changes and new gene formation. I recently published a study titled "Excess of genomic defects in a woolly mammoth on Wrangel Island" with Montgomery Slatkin. We reanalyzed genome sequences for two woolly mammoths. One specimen came from Siberia at a time when mammoths were happy and healthy. The other comes from a small population that existed on Wrangel Island until 3700 years ago, another 600 years after all mainland mammoths had gone extinct. We found that bad mutations were accumulating in woolly mammoth genomes just before they went extinct. The accumulation of bad mutations is consistent with mathematical theories predicting that natural selection becomes inefficient in small populations. Under these circumstances, bad mutations could accumulate in genomes that normally would be weeded out by competition. The mammoth from Wrangel Island had 50% more of its genes broken compared with the mainland mammoth from much earlier. Several different types of bad mutations had accumulated— large deletions in the DNA, retrogenes (which reflect the action of selfish virus-like DNA sequences), and single letters that would cause genes to terminate early. Many of the broken genes are urinary proteins and the olfactory receptors that detect them — genes important for social signaling. We also discovered that the mammoth from the island had mutations that would give him a shiny satin coat. These results may be important for conservation. They suggest that other very small populations of endangered species might undergo the same type of mutational meltdown. In our mammoths, we found that it required many generations to see a signal as strong as what we observed in the Wrangel Island genome. The sooner we can intervene to bring endangered species back to normal levels, the better off their genomes will be. There are many factors that influence extinction. Climate change, habitat destruction, and hunting were all very important for the mammoths' demise. Still, these bad mutations certainly did not help them as the struggled to adapt on the island. Listen to the 60 second Science podcast on our work. I will be answering your questions at 1pm ET. Ask me Anything! Don't forget to follow me on Twitter @evolscientist or elsewhere on reddit as rlrogers. Alright! 1pm ET! Ready to go! Ok, thanks for all the fun questions!! I had a great time! Now it's back to the lab to collect fruit flies!

the
WINNOWER

REDDIT

PLOS Science Wednesday: Hi reddit, my name is Rebekah Rogers and I found that, before extinction, two different species of woolly mammoths had bad genetic mutations, which likely didn't help their survival -- Ask Me Anything!

PLOSSCIENCEWEDNESDAY R/SCIENCE

Hi Reddit,

My name is Rebekah L. Rogers and I am an Assistant Professor in the Department of Bioinformatics at UNC Charlotte. My research focuses on genome structure changes and new gene formation.

I recently published a study titled “Excess of genomic defects in a woolly mammoth on Wrangel Island” with Montgomery Slatkin. We reanalyzed genome sequences for two woolly mammoths. One specimen came from Siberia at a time when mammoths were happy and healthy. The other comes from a small population that existed on Wrangel Island until 3700 years ago, another 600 years after all mainland mammoths had gone extinct.

We found that bad mutations were accumulating in woolly mammoth genomes just before they went extinct. The accumulation of bad mutations is consistent with mathematical theories predicting that natural selection becomes inefficient in small populations. Under these circumstances, bad mutations could accumulate in genomes that normally would be weeded out by competition. The mammoth from Wrangel Island had 50% more of its genes broken compared with the mainland mammoth from much earlier. Several different types of bad mutations had accumulated— large deletions in the DNA, retrogenes (which reflect the action of selfish virus-like DNA sequences), and single letters that would cause genes to terminate early. Many of the broken genes are urinary proteins and the olfactory receptors that detect them — genes important for social signaling. We also discovered that the mammoth from the island had mutations that would give him a shiny satin coat.

These results may be important for conservation. They suggest that other very small populations of endangered species might undergo the same type of mutational meltdown. In our mammoths, we found that it required many generations to see a signal as strong as what we observed in the Wrangel Island genome. **The sooner we can intervene to bring endangered species back to normal levels, the better off their genomes will be.** There are many factors that influence extinction. Climate change, habitat destruction, and hunting were all very important for the mammoths’ demise. Still, these bad mutations certainly did not help them as the struggled to adapt on the island.

Listen to the 60 second Science podcast on our work.

I will be answering your questions at 1pm ET. Ask me Anything!

Don’t forget to follow me on Twitter @evolscientist or elsewhere on reddit as rlrogers.

Alright! 1pm ET! Ready to go!

Ok, thanks for all the fun questions!! I had a great time! Now it's back to the lab to collect fruit flies!

READ REVIEWS

WRITE A REVIEW

CORRESPONDENCE:

How do you know what mutations are bad and which aren't without an actual living population to observe the effects of the mutation ? Can you read DNA analog to reading the machine code of a computer program and spot 'bugs' in the code or are there other ways ?

DATE RECEIVED:
April 13, 2017

DOI:
10.15200/winn.149200.01480

ARCHIVED:
April 12, 2017

CITATION:
PLOSScienceWednesday , r/Science , PLOS Science Wednesday: Hi reddit, my name is Rebekah Rogers and I found that, before extinction, two different species of woolly mammoths had bad genetic mutations, which likely didn't help their survival -- Ask Me Anything!, *The Winnower* 4:e149200.01480 , 2017 , DOI: 10.15200/winn.149200.01480

BorgDrone

We know where the genes are in the African elephant genome. We can then go look at the mammoth DNA, match it up with African elephants, and see which spots in the genome have mutations that use different letters, or mutations that take a chunk of DNA and delete it or move it around. Deletions, which just take out big chunks of DNA can break gene sequences. We know that generally breaking genes is a bad thing.

Some single letter changes may have no effect because they do not change the protein sequence. Other single letter changes may break the gene and stop protein production part-way through. We know that these mutations that break genes are usually bad. A third class of mutations may change the protein sequence but not break it completely. It can be difficult to tell the impacts of any single amino acid change just from looking at the sequence.

We know that as a class it would be unusual to have tons of these mutations genome wide compared to another individual in the same species. It would also be unusual to have an excess of bad mutations across multiple classes (deletions, retrogenes, and point mutations).

Genetically speaking, what was the worst thing old Woolly had going against him?

GreatScotch

Our study was whole genome and high throughput. There are some mutations where we were certain enough about exactly what the genetic change was AND the genes do the same thing in multiple types of animals. These are mutations in riboflavin kinase, FOXQ1 (the satin locus), urinary proteins, and olfactory/pheromone receptors. There are other bad mutations in the mammoth, but with some of them we couldn’t nail down exactly where the breakpoints were. Some of the uncertainty is related to working with ancient DNA, and some simply requires doing focused work on just those gene sequences.

Some suggest that this mammoth may have had terrible diseases or that he may have had difficulty reproducing. It will take some more work to say exactly which of those are real and what the exact nature of those mutations might be. If even 10% of those were real, this mammoth had problems.

What animals are currently in a similar situation where they risk the same degradation due to small isolated population ?

lizardbrains

Cheetahs, pandas, rhinos, mountain gorillas, basically anything on the critically endangered species list. The good news is that the severity of genomic meltdown will depend directly on how much time the population size is reduced. The sooner we can intervene to bring animals back to normal levels, the better off they will be.

When will we see a live wooly mammoth? Science keeps promising.. all we get is fancy gifs here.

beatvox

George Church has suggested genetically engineering an elephant to look like a mammoth. They are first screening mutations in cell lines and in mice to see what their effects are.

Generally genetic engineering studies would only mutate one gene at a time. The gestation time for an elephant is 1 yr, and the generation time is minimum 15 years. Take your best guess about how many genetic changes you would need, and multiply that by 16 yrs. I'm not ordering a mammoth saddle.

How attributable do you think these mutations were to inbreeding? Was the population small enough that you suspect it as a culprit?

scoobyspelly

The mammoth from Wrangel Island was somewhat inbred, not from siblings but from matings between distant cousins. This analysis was presented in Palkapoulou et al 2015, along with the sequence data. Inbreeding leaves different genetic signatures compared with genomic meltdown. It increases the likelihood that a single individual carries recessive detrimental mutations at the same locus, causing bad effects. If both mom and dad are related and carry the same bad mutation, it’s more likely that their offspring will look like mutants than if they mate with a random individual (who is less likely to carry the bad mutation). This phenomenon would show in the genome as lots of sites that are homozygous—where the chromosome from mom and the chromosome from dad look identical.

We saw that in small populations, bad mutations accumulated across the entire genome as natural selection became less efficient. We saw an increase in mutations that would break gene sequences in the small population, then did mathematical modeling to show that these effects were consistent with expectations of how bad mutations accumulate due to genetic drift. The accumulation of bad mutations genome wide across many different genes is the product of genomic meltdown. At the FoxQ1 gene we even saw two bad mutations in the same gene but with different origins. This would not happen with inbreeding.

Has this genetic behavior been noted in any other species, past or present? If so, how have those species fared?

How can we tell this behavior is detrimental? It seems urinary and olfactory signaling were dying out while a shiny satin coat were introduced might they just have shifted from one method of mate selection to another?

techniforus

The best case that I know of for similar genetic meltdown is in the foxes on the Channel Islands. They found that there were lots of amino acid changes accumulating in the foxes on the island, which has had a similarly small population for a very long time. We would be very interested in following up on the foxes to see whether they have a similar excess of other classes of mutations, and how good the fit is with mathematical models of genomic meltdown.

Other people are starting to sequence other endangered animals (yes, like Cheetahs). I will be very interested to see what comes of it.

How do you feel about the US government (and others) destroying environmental data and protection laws? In the long run, how do you feel this will affect current species, endangered and not endangered, and even humans? Secondly, do you think it would theoretically be possible to 100% reverse the damages humans have done to the world, and why?

JustNotGrunge

Generally scientists like data. We like keeping data once we have it. It helps us understand the world around us and make informed decisions.

The ethics guidelines established by the NIH for biomedical research state that destroying data (before or after publication) should always be investigated. No matter what the policy is on environmental protection, destroying the data that informs policy decisions is wrong.

There was a great story about a hack-a-thon at Berkeley that saved large sections of EPA data. I was glad to see that.

Can you describe how confident anyone can be when sampling just two individuals (one from each location)? How is there enough information present to make any broad conclusions about genetic diversity and mutational load? It seems that with just two individuals, most expectations of population-level metrics break down.

EDIT: ok, one more question--now that I think about it, I also don' t understand how*any* heterozygosity measures here can be considered reliable? Both of the mammoth genomes were sequenced on Illumina machines at what most would (subjectively) call only medium-low coverage for a diploid (11x and 17x). Given the Illumina sequencer's error mode is one of erroneous nucleotide *substitutions*, it really seems like any apparent heterozygosity could just as likely be sequencing error as "real" variation. How robust do you think the mammoth genome data really is to such errors?

EDIT2: and I'm not meaning to seem like a jerk. Genuinely interested in learning about evolutionary popgen!

RabidMortal

These are great questions.

With only two samples to analyze, we had to use theory and mathematical modeling to tell us whether the differences we saw were too extreme to be explained by variation within a population. There are very well established theories to explain how much variation should be present in a population. Based on these theories, the two mammoths were 28 standard deviations apart— much too extreme for them to have come from the same type of population. We then showed that in small population sizes, we would expect an accumulation of negative mutations similar to what we saw in the Wrangel Island mammoth. Without this mathematical modeling, we would not have been able to make the same conclusions.

We also saw that all different types of mutations pointed in the same direction. The Wrangel Island mammoth had an excess of amino acid changing mutations, an excess of premature stop codons, an excess of deletions, an excess of deletions affecting gene sequences, and an excess of retrogenes (reflecting transposable element activity). It’s pretty rare in my experience to have such a massive difference AND to have the same signal in every type of mutation.

With respect to sequencing, the error rate for Illumina is pretty low, but we wouldn’t expect error from the sequencer to affect one sample that much more than the other. We did check to make sure the differences in mutations weren’t artifacts of differences in coverage or differences in DNA damage. We specifically limited the analysis to large deletions because smaller deletions are more likely to be artifacts. But yeah, there was a lot of angst and extra analysis trying to make sure the effects that we saw weren’t just a fluke.

Is the difference in hair a functional change?

itrv1

We know that the mutations at FoxQ1 should change the fur structure and produce the satin phenotype, as long as this gene acts the same way in mammoths that it does in other mammals. Mammoths had very stiff outer guard hairs that helped keep the snow off. Paleontologists have suggested that the inner core of the furs was very important for mammoths in generating these coarse hairs. Other paleontologists have argued a bit over the fine details of their claim. If the stiff core was an adaptation, then yes, this mutation would compromise that adaptation.

We also know that the same gene helps replenish cells in the stomach as they are eroded by stomach acid. Satin rabbits often need special diets because they have GI issues. It seems likely that the mammoths would have had similar problems with heartburn.

How are you able to tell what each gene does to thrn be able to categorize it as a good or bad gene? Has enough of the mammoth genome been mapped and how comparable is it to an African or Asian elephant? Lastly, what are your thoughts on the possible de-extinction of mammoths and other animals that could be brought back through gene manipulation?

sonofabish26

Woolly mammoths are closely related to Asian elephants, and African elephants are more distant relatives. We mapped all the mammoth DNA onto the African elephant Loxodonta africana genome. The two are a surprisingly good match.

I recently read about a Russian group that are trying to create a population of mammoth-like creatures to help reduce the melting of Siberian permafrost and hence climate change. These mammoths would be made by modifying the genes of Asian elephants and incubating them in the lab.

Firstly, how similar could these be to historical mammoth? Is the limit theoretical or 'only' technical?

Do you think that if we were confident that this would be effective in reducing further global warming it would be a good idea?

The reasoning wasn't so clear in the article, but from what I could tell, mammoth would eat away at the treeline which would result in more grassland, which reflects more sunlight than forest, which would reduce permafrost melting. Do you have any thoughts on this? To me it seems like logging and introducing grazers would be enough to have the same effect (and grazers are an existing part of the proposal). But I suspect I missed part of the argument. Are mammoths really good at killing trees?

Finally, is the topic of bringing back mammoths something you get tired of, laugh at or dismiss entirely?

Here is a link to the article from this month's Atlantic.

climb026

Woolly mammoths could not eat trees. Their teeth are flat with shallow ridges that ground up grasses, similar to Savannah elephants. This is one of the factors that contributed to their extinction. As forests grew up over the Siberian grasslands, the mammoths struggled to find food. Combined with human predation, their numbers dwindled. Mastodons have a completely different tooth structure, with sharper points. Their name even means “nipple toothed”. Mastodons (and possibly Columbian mammoths) could eat twigs and bark, but woolly mammoths could not.

Wrangel Island is an unusual habitat. It does not have grasslands, but scrubby bushes. The island gets hit periodically with arctic cyclones. These storms rip up trees and prevent them from growing on the island. The cyclones make Wrangel Island a harsh environment to live in, but in the end they may be one reason why the mammoths could persist on the island even after the mainland populations were extinct.

... which reflect the action of selfish virus-like DNA sequences

What makes a DNA sequence "selfish", and how does it differ from sequences that are not selfish?

antonivs

Transposable elements are selfish genetic elements that live in the genomes of most eukaryotes. They copy themselves like viruses, even if it causes harm to the host. There is constant conflict over evolutionary time. TEs will proliferate and cause bad mutations, the cell will come up with a repressor to keep the TE quiet, and then the TE will mutate again to proliferate. It's a genetic arms race that leads to some pretty exciting biology.

If you've read Dawkins' the selfish gene, this exactly the type of dynamic he is talking about.

Do you think that one day, we will be able to find Homo neanderthalensis DNA in good condition ?

PM_ME_YOUR_HEELS

They have!! Two neanderthals have been sequenced to high coverage. This is how they know Neanderthals and humans interbred. It also helped people trace their migrations out of Europe as separate events.

I have other work on genome structure changes in Neanderthals, which was an interesting project to work on.

Roughly how much satin would that shiny mammoth produce? In a year? In its life?

CousinLaban

Fun question!!

I’m not 100% sure but I’ll give you my back of the envelope calculation. I read that the average satin rabbit produces 12 oz of wool per shearing. Let’s say they are ~6 in tall, compared with a mammoth that is 12 ft tall. 12 /.5 * .75= 18 lbs of fur.

Or comparing with sheep 5 lbs of wool per sheep and they are about 3 ft tall. 12/3 *5 = 20 lbs. So I’m going to say roughly 20 lbs per shearing. (Sheep bred for fur may have much greater yields, I'm going with numbers closer to wild sheep.)

Mammoths had stiff guard hairs to keep the snow off. Rabbits with guard hairs are not considered ideal for fur, so I’m not sure how much would actually be useful. Note that none of these calculations have passed peer review.

It does add to the mystery of why no one domesticated the mammoths. Feel free to contribute your own estimates.

Hey! I'm a Mechanical Engineering Student at UNC Charlotte, and I spend my time across the street in Duke Centennial, so hello from the other side. Now, you mentioned that the accumulation of bad genes occurs over several generations in a small population, and that this may have a hand in conservation of endangered species. Does this mean that there could be a point of no return where the species can no longer recover genetically, or is it possible for natural selection to begin to sift out the bad genes again given a sufficient boost in population?

JTB54

We would expect that a population, once brought back to large population size, would purge some of the bad mutations. There is a nice paper with this theory from Balick et al. (link below). This purging will take a VERY long time.

With the large deletions that we studied it will be even more difficult to undo the damage. Once a gene is completely deleted, how do you get it back? Most of my research is on new gene formation. It is much more difficult to get new beneficial genes than it is to repair a single letter change in the DNA. There could be other compensatory mutations, but that's difficult to guarantee.

http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1005436

Is there many other species of wooly mammoth? Would it be hard to prove that they all contained some badly mutated genes?

geneticsrus

There are several different mammoth species. Woolly mammoths are one. There were also Steppe Mammoths, Columbian mammoths, Southern Mammoths. There were a few subspecies or groups on islands as well-- Wrangel Island, St Paul's Island, Channel Island and Crete.

Do you see any similarity with the human species?

TechnoYogi

Some people have hoped to find evidence of mutations accumulating especially in small groups of archaic humans. So far, no one has found a signal as strong as what we saw in mammoths. The mammoths were a very extreme case with a 43 fold change in population size and they were isolated for thousands of years. There might be less extreme cases in humans that could be found with more individuals and more complete theories, but nothing has come up yet.

That's fascinating. Do you know how/why the mutated population was isolated as it was?

yobsmezn

Mammoths went back and forth from the mainland to the island when glaciers covered the Siberia and sea levels were higher. The mammoths became isolated on the island as sea levels rose. There's some debate about the exact timing but we know that by 12,000 years the mammoths were only on the island.

There's some debate about how far the mammoths could swim in the arctic, and also about how think the ice sheets were in winter vs summer months. By 12,000 years ago the channel between Wrangel Island and the mainland was too wide for them to cross. Thankfully it kept the humans away for a long time as well.

I have an unscientific question.

What got you interested in studying ice age animals, and Wooly Mammoths in particular? Aside from the Ice Age movies, that era of earth's history doesn't seem to get a lot of love in the mainstream.

TheVantasy

I've wanted to work on mammoths since Kindergarten. I had heard about arctic explorers who found mammoths frozen in ice sheets with fur still on them. To me it seemed like the closest you could get to having a time machine. We could still see what these animals looked like even tens of thousands of years after they had died off.

When Love Dalen's lab published these mammoth sequences, I downloaded them the same day. It was exciting to get to work on mammoths, but even more exciting when I saw what looked like a genomic meltdown. It's probably one of the more fun projects I've worked on.

G'day Rebekah,

The social signalling "confusion" seem quite fascinating.

Any insight into whether this would of been exhibited by things such as increased violence against other Mammoth? Is it possible that this produced "poor" mating choices by the mammoth herds? (Such as preventing or at least suppressing the mixing of mammoth herds)

Thank you for your time.

I apologise for my ignorance of mammoth if these questions seem too silly.

cardboard_box_robot

It's difficult to say what the exact effects might be using gene sequences alone, but any of these are possible. Better research on urinary proteins and olfactory receptors in elephants might help us figure out more detailed answers.

had 50% more of **it's** genes broken

twitch

Ripcord

Repaired. Thanks.

How did y'all conclude that the mammoths had a shiny satin coat? Compare the DNA to other animals? A computer program that can project phenotype from a genotype?

Aximill

There are two mutations in a gene called FoxQ1. One chromosome has a frameshift mutation-- an extra site gets put in and it messes up formation of the protein completely. The other chromosome has a huge deletion that takes out the entire gene.

That gene causes a satin coat in mice, and it's involved in fur formation in other mammals. So long as the gene acts the same way in mammoths that it does in lots of other mammals, the mammoth would have a very shiny coat.

It's a bit of a stretch, seeing as I don't know if you've ever touched any, but what does mammoth fur/hair feel like?

commander_cuntmunch

The outer guard hairs were very long and stiff to keep out the cold. Underneath were a much softer fur. I have some, along with mammoth ivory on my book shelf.

I have access to a mammoth skeleton found in the 1840s. Is there funding available to have it tested?

PortraitsofWar

If it came straight from permafrost, there's a chance it has DNA good enough to be sequenced. If it was buried outside the arctic chances are slim. Most mammoth sequencing is happening at UCSC, the Swedish Museums of Natural History, and formerly at Penn State.

Why do you think these mutations occurred?

Shahidsp

Mutations appear at random over time. Bad mutations are removed from populations as long as the population size is very large. When population sizes are small, chance plays a bigger role. Mutations that might be out competed are tolerated in small populations. This leads to an accumulation of bad mutations in the genome.

Is it safe to assume that the olfactory defects happened because 1. Climate got hotter therefore smells smell different 2. As with 1 smells on an island must be different to mainland and 3. a small population condensed on an island wouldn't have any need to smell other herds at great distances?

Also, is there any evidence that atleast suggests humans ever tried to domesticate mammoths anywhere?

Krabice

Any of these could be true. It could be that selective pressures changed-- predators weren't found on the island, the plant composition was different, perhaps there was less sexual selection. It could equally be true that breaking olfactory receptors just isn't that bad. It's not as if the mammoth drops dead when one olfactory receptor is broken. So it falls within the neutral threshold and the mutations start to accumulate.

How do you compare the wooly mammoth's genetic mutations with that of humans?

TechnoYogi

Most genes in humans have a direct match in other mammals. Even more broadly across the tree of life, we know that 77% of disease genes in humans have a direct match in fruit flies. One recent experiment showed that if you replace a fruit fly gene with a human gene, 70% of the time the flies would still live. We can compare the DNA sequence and the protein sequence between mammoths, mice, humans, and flies to match up the different genes and functions. This is one of the reasons why research in model organisms is so important. It means that if we find an effect in mice or fruit flies, it is likely we will observe similar effects in other organisms, including humans.