

Science AMA Series: We are Mollie Woodworth and Michael Lodato (Harvard). We sequenced single neurons from normal human brain and found ~1700 mutations per neuron. We're here to talk about these “soma

*somatic mutations*<sup>1</sup> and *r/ScienceAMAs*<sup>1</sup>

<sup>1</sup>Affiliation not available

April 17, 2023

### Abstract

Ongoing, random mutation to DNA ensures that no two cells in an individual are genetically identical. Since mature neurons can survive for the lifetime of an individual, their DNA is exposed to mutagens (oxygen free radicals, electromagnetic radiation, endogenous transposable elements, etc.) on an ongoing basis. These forces have the potential to induce somatic mutations, and potentially contribute to normal aging and neurodegenerative disease. We sequenced single neurons from normal postmortem human brains to identify rates and patterns of somatic mutations published in the October 2nd issue of Science, layman's summary at The Atlantic Most of the mutations we identified are unique to a single neuron, and we can use them to say something about the kinds of mutational processes that impact a neuron's genome. Many of the mutations appear to have happened during the process of gene transcription, which is unfortunate, because it means that the genes a neuron needs most and uses most often are those that are most likely to be mutated. A small fraction of the mutations are shared among multiple neurons. Since neurons don't divide in the brain after about week 20 of fetal development, we know that those shared mutations happened during embryonic and fetal development in progenitor cells, and then were passed on to their progeny. We can use those shared mutations as tags to mark particular lineages of cells in brain development, much in the same way that we can use viruses or other markers as tags to mark lineages in experimental organisms. Because somatic mutations in the brain represent a durable and ongoing record of neuronal life history, from development through post-mitotic function, our work enables us to make a lineage map to identify family relationships between cells in the brain. tl;dr Mutations are happening in your neurons every day! We looked at individual neurons to find out how many. EDIT: Thanks so much for all your thoughtful questions, and for the great discussion! We had so much fun doing this today.

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# Science AMA Series: We are Mollie Woodworth and Michael Lodato (Harvard). We sequenced single neurons from normal human brain and found ~1700 mutations per neuron. We're here to talk about these "soma

SOMATIC\_MUTATIONS [R/SCIENCE](#)

## ABSTRACT

Ongoing, random mutation to DNA ensures that no two cells in an individual are genetically identical. Since mature neurons can survive for the lifetime of an individual, their DNA is exposed to mutagens (oxygen free radicals, electromagnetic radiation, endogenous transposable elements, etc.) on an ongoing basis. These forces have the potential to induce somatic mutations, and potentially contribute to normal aging and neurodegenerative disease. We sequenced single neurons from normal postmortem human brains to identify rates and patterns of somatic mutations [published in the October 2nd issue of Science](#), [layman's summary at The Atlantic](#)

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A small fraction of the mutations are shared among multiple neurons. Since neurons don't divide in the brain after about week 20 of fetal development, we know that those shared mutations happened during embryonic and fetal development in progenitor cells, and then were passed on to their progeny. We can use those shared mutations as tags to mark particular lineages of cells in brain development, much in the same way that we can use viruses or other markers as tags to mark lineages in experimental organisms. Because somatic mutations in the brain represent a durable and ongoing record of neuronal life history, from development through post-mitotic function, our work enables us to make a lineage map to identify family relationships between cells in the brain.

**tl;dr Mutations are happening in your neurons every day! We looked at individual neurons to find out how many.**

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## CORRESPONDENCE:

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**Cool study. We are just starting to grasp variation in genomic architecture between individuals, so it was really interesting to see a study look at intra-genomic variation. A couple of nitty-gritty questions:**

- 1. I was surprised to see that enrichment of exonic SNVs in neurons reached significance. It looked like SNVs mapped to exons about 1.3-1.4% of the time in your study, with a fair bit of variation -- that seems just about what I would have expected based on the fraction of the genome that is exonic (about 1.1 - 1.4%). It seemed to me, though, that intronic mutations are certainly enriched in your sample. Is it possible that the cells are employing exon-specific DNA repair mechanisms?**
- 2. If transcription is truly a risk-factor for mutation, I would have hypothesized that highly transcribed genes, not neural genes would have been enriched in SNVs taken from your**

Mollie Woodworth and Michael Lodato (Harvard). We sequenced single neurons from normal human brain and found ~1700 mutations per neuron. We're here to talk about these "soma", *The Winnower* 2:e144404.46810, 2015, DOI: [10.15200/winn.144404.46810](https://doi.org/10.15200/winn.144404.46810)

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**brain samples. Why do you think you are seeing more mutations in neural genes rather than highly transcribed genes (i.e. ribosomal gene products, housekeeping genes etc.)?**

- 3. You mention in the text that you observe L1 insertions, but I didn't see a quantification of how many were observed across nuclei. There is considerable debate in the field about how abundant L1 insertions are in the neurons, with estimates ranging from a few per nuclei to hundreds. What were your observations? Also, L1s are highly transcribed, especially in neurons, did you see high mutation rates in these loci? Or were they too difficult to map in your analysis?**
- 4. It looks like most of your mutations are in intergenic regions. Do you see a bias towards transcribed intragenic DNA (i.e. L1, Alu etc.) or is it non-transcribed intragenic DNA (centromeres, telomeres, spaceholder etc.)?**

**Thanks!**

**[SirT6](#)**

Thanks! We agree that we have a lot to learn in terms of both inter- and intra-individual variation.

1. You're right that we observed ~1.4% of the SNVs in exons, and the expected was about 1.1%. After controlling for lots of variable, we were able to confidently say this slight but statistically significant enrichment in exons is there. Introns were also enriched in all three individuals, but not statistically significantly so in all, so we focused more on exons. Whether these is differential repair in exons vs. introns is unknown, but would not be impossible.
2. Great question. It's possible that very highly transcribed genes more efficiently recruit the repair machinery, since they are the most prone to damage. We're not exactly sure. One thing to note is that in our oldest individual, a 42yr old female, the highest expressed genes had the most mutations, so there could be variation between individuals.
3. The L1 insertions were profiled in two great previous papers from our lab (<http://www.ncbi.nlm.nih.gov/pubmed/23101622> and <http://www.ncbi.nlm.nih.gov/pubmed/25569347>). Estimates from these studies suggest somatic L1 insertions in the human brain are very rare (much less than 1 per genome). We did not look directly at endogenous L1 loci to measure the SNV rates at these sites, but it would be cool to look into in the future!
4. See answer 3 for the transposon stuff. We saw that open chromatin in general was enriched for mutations, active enhancers would be another set of loci which might accumulate damage at high rates.

**Hi, thanks for the AMA.**

**Couple of quick questions:**

- 1. Is there any indication of hypothesis that this mutation could perhaps be directed to some extent, as in homologous recombination in immune cells?**
- 2. Since everyone is wanting to know, how does this level of mutation occur to difference between other somatic tissues?**

**Thanks!**

**[duckpearl](#)**

1. We don't have any evidence that the mutations are directed, or that they are part of any mechanism to intentionally generate genomic diversity. But we are definitely just looking at the tip of the iceberg

here -- we sequenced 36 cells from 3 individuals -- so it will be really interesting to see what we missed in this initial sweep.

2. There haven't been many studies looking at rates of mutation in normal cells. It has only been possible to look at mutations in single cells very recently, so previous studies were mostly focused on sequencing big chunks of tissue, often tumors. We do find similar numbers of mutations as a study looking at [normal kidney cells](#), although our methods are a little different. We might predict that brain and other tissues composed of non-dividing cells would have slightly lower rates of mutation than actively dividing tissues, like [skin](#) or blood.

**Do mutations of the neurons hinder their ability to function? Have you found any that may have increased their productivity?**

[Henrymeister](#)

We couldn't directly say if any mutations altered the function of the neurons in which they occurred, however we did observe mutations that, had they been present in all the cells of the brain, would have caused diseases including schizophrenia and intellectual disability. Also, we know that some human neurological diseases, like epilepsy, are sometimes caused directly by somatic mutations, so understanding this process is important for human health.

**I haven't formally studied much science past high school but it does fascinate me that we are on a track to discover new ways to understand how our brains work. Can you elaborate on making "a lineage map to identify family relationships between cells in the brain"? Could this kind of mapping help neurologists find new connections/active relationships between areas of the brain, ones that we don't intuitively think of as connected? Or is there some other implication of these "family relationships" that you are most interested in?**

**Thank you for your time.**

[barnufus](#)

As you said, we were able to make a lineage map of relationships between cells in the brain using these mutations.

Most of the mutations we found were only found in one single cell, so we suspect they occurred in adulthood. These "unique" mutations were not useful for lineage mapping.

We also found some "shared" mutations, meaning mutations which were present in many, but not all, cells. It is using these "shared" mutations that we could make lineage maps of cells in the brain. "Shared" mutations must have happened in a stem cell some time during fetal development, and then been passed on to every daughter cell descending from that original mutated stem cell. So, if we have a set of 50 cells which all have Mutation A, we know they are all related to each other and descended from a common ancestor cell that had Mutation A. If another set of 50 cells has Mutation B, but not A, we know that we have 2 branches of a tree, one starting with a cell which had Mutation A but not B, and another branch derived from a cell with Mutation B but not A.

We were able to identify 4 such branches in one of the individuals we studied, plus cells which were not in any of these 4 branches, meaning there are at least 5 branches of cells. We could even divide the cells up within these branches. For example, if of the 50 cells with Mutation A, 20 had mutation A.1, we could say those 20 derived from another stem cell, which inherited Mutation A, then acquired mutation A.1. One branch we found was composed of 11 such mutations! Each in progressively less and less cells.

**What implications do such mutations have on things like learning and cognition?**

[kamronb](#)

We don't hypothesize that the mutations are the result of a directed process to encode memory. We did not find any evidence of this whatsoever. They are the byproduct of random DNA damage.

**That's a huge number of mutations per neuron (which is just one cell, right?). How do the mutations affect the functionality of the cell? At what point, in terms of the number of mutations, does the neuron stop doing its job?**

[9999monkeys](#)

It's a big number, but each cell also has a really big genome!

The vast majority of the mutations are in non-coding regions of the genome, and probably don't have any effect on the function of the genome or of the cell. We did find some mutations that are in known disease genes (that is, if that mutation were in the germline, it would cause a disease; in this case, intellectual disability), and we would predict that those neurons would be functioning less efficiently than their non-mutated neighbors.

**Do you have plans to sequence glia in addition to neurons to help draw conclusions about whether the progeny of radial glia are restricted to certain cell types innately or if they are truly tripotent?**

[tofuyasan](#)

That's definitely up there on the list of experiments to do! It's a really interesting question, and one that we could absolutely address with these methods.

Practically, we're somewhat limited by the antibodies we can use to sort different cell types -- since we sort nuclei, the antibodies we can use need to be to proteins that are a) abundant, and b) in or on the nucleus. Another group (the one that originally developed this nuclear sorting method) recently published [a paper](#) where they used a Sox10 antibody to sort adult glial nuclei, but we haven't gotten the antibody to work in our hands yet.

**Hi Mollie, huge fan of your work. So you've learned this really cool thing-- I guess my question is-- how do you use this knowledge? In what ways (if any) does this empower scientists or physicians in treating, preventing, or predicting brain diseases? Thanks again for coming to see us at [/r/science](#).**

[Inri137](#)

Timur, you only ask the small questions, don't you?

I think we're beginning to realize that some diseases that have previously been thought to be only germline in origin actually have a substantial number of cases that are somatic. So there are many people -- including a large number of kids who come through our hospital and are enrolled in our genetic studies -- who are suspected of having a particular disorder or syndrome, but whose genetic testing (which is usually done on blood samples, not brain samples, for obvious reasons) doesn't bear out that diagnosis.

Our lab [published a paper last year](#) saying that you can sometimes find these somatic mosaic mutations in blood, as long as you sequence deeply enough. And our analysis bears that out -- we identified a number of mutations in single neurons that we could also find in other organs across the body, even organs that are quite developmentally removed from the brain. We think that something present at a high enough frequency to cause brain disease is probably generally also present in tissues outside the brain. This suggests that a lot of cases of disease could be solved simply by sequencing more deeply, which is great news for the kids and families who come through our lab and

labs like ours.

**So, 1700 mutations per neuron cell per lifetime (ie. generation) has some serious implications for how our DNA is degrading over time and over generations.**

**Q1. Were you able to determine how many of the mutations were harmful, how many neutral, and how many beneficial?**

**Q2. I assume that many of the harmful mutations would just have killed the neurons, so this means that you have actually underestimated the number of mutations, since you're only looking at living neurons. Correct?**

#### [MRH2](#)

We agree. We found a small subset of mutations in coding regions (~1.4%, 20-25 per genome), but we don't know if any were functional. Our study supports the idea that functional mutations might accumulate in normal brains and cause phenotypes. The chances of these being beneficial in any way are very very small. One way to think about this is if you had a Swiss watch in perfect working order, and you tapped it lightly with a hammer, what are the chances you would make it run better? What are the chances you'd break it? The latter is much more likely. In this metaphor, your DNA would be the watch.

You're right that very deleterious mutations would not be detected, since the cell would have died. We did not observe a strong signature of selection in our dataset, so we believe this phenomenon was minor.

**The real breakthrough in this paper seems to be that we now have a possible way to do clonal analysis in human cell lineages. In the Atlantic summary Walsh speculates as to the reason why cell lineages during development seem to end up in very different organs and suggest that it might be an evolutionary advantage to have your brain come from more than one or two embryonic clones.**

**Would you predict that protostomes have a higher rate of organ failure than deuterostomes, since they have determinate growth with predetermined cell lineages?**

#### [Hypatio](#)

Agreed, the human lineage tracing is a huge breakthrough.

An animal like *C. elegans* probably does to fall victim to a "putting all your eggs in one basket" in terms of their deterministic development. If you laser-ablate a progenitor cell in a developing worm its progeny don't form, so presumably if these cells acquire deleterious somatic mutations the result would be the same.

**I'm starting a research project with a professor focused on mutations and their link to cancer. It's really cool to see this up on the front page right around the same time that we had a conversation about normal cells with large amounts of somatic mutations. What do you guys believe/know is required to change these normal cells with somatic mutations to cancerous cells?**

#### [Tipe O](#)

Probably not surprisingly, we did not find any canonical cancer causing mutations in these cells. Most seemed to have no functional impact. Likely each somatic mutation is like a lottery ticket, and it is just blind luck whether it hits a gene desert or a tumor suppressor.

**How will this impact future simulations of neurons and biologically accurate neural networks, if at all? Is this a major stumbling block on the way to a whole brain simulation?**

[Lawls91](#)

I've been thinking about this for a while, and I think no, it won't be a problem for accurate simulations. I think the bigger problem for accurate simulations is that this isn't the only complex, difficult-to-predict factor with small differential effects on the behavior of individual neurons in large circuits.

In short, I think the problem is so big that this isn't the biggest stumbling block out there.

**Is there any mutation pattern within the neurons that belong to the same regions of the brain ?  
Thanks in advance.**

[Chacha-Choudhry](#)

Yes, we found a series of mutations whose range was progressively more restricted to the frontal part of the brain -- earlier mutations in this series were present across the brain and the body, and later mutations were more and more restricted to frontal cortex.

I put the relevant figure piece [here](#), on Imgur -- you can see that as you go down the blue section of the tree on the left, the mutations are more and more narrowly distributed on the right.

**What are the most useful potential practical applications of this technology?**

[wolark](#)

When people think about DNA testing, we think of taking some blood, harvesting DNA, and sequencing it to get a sense of the mutations that person might have inherited and led to disease.

Based on our work and the work of many others in this field, we now appreciate that the genome of cells in one part of the body might be very different from that found in another part. Therefore, it is possible that a person with a neurodevelopmental disorder might exhibit no harmful mutations in a blood-DNA test, but in fact the disease could be caused by a mutation that is restricted to (or at least highly enriched in) the cells of the person's brain.

The good news is our data suggested that mutations that were in a large fraction of cells in the brain (5-10%) we often also found outside the brain. If we assume that there has to be a large number of cells with a pathogenic mutation in the brain to cause disease, this suggests that if we sequence someone's blood very deeply, we might indeed find rare mutations causing neurological disease.

**What mediating effect might this have on individual variations in neuropharmacodynamics?**

[fuckyoudrugsarecool](#)

We think that somatic mutations could dampen or amplify the effect of inherited mutations -- that this might be part of why things like pharmacodynamics are so variable from person to person.

**Do you think this has anything to do with neuron organization (axon/neurite repulsion)? Similar to what DSCAM does in Drosophila?**

[daemonk](#)

Not likely, since the mutations were mostly randomly distributed throughout the genome.

**Do mutations occur at faster or slower rates in response to stimuli. For example if someone were to undergo some form of electro-convulsive therapy or something where an electric**

**current is 'zapped through our nervous system' briefly, would the neurons start mutating faster or slower due to some unknown mechanism?**

[journeyond](#)

It's certainly a possibility, and something that we're interested in addressing in the future. For example, some parts of the brain undergo neurogenesis in the adult, and rates of neurogenesis are known to be affected by external stimuli (including electroconvulsive therapy, exercise, stress, and others). We are interested in finding whether those areas of the brain have higher or lower rates of mutation.

**Could your research be relevant to the study of the possible mechanisms underlying Autism Spectrum Disorders?**

[chemotaxis101](#)

Absolutely! Actually, one of the MD/PhD students is studying the role of somatic mutation in autism spectrum disorders, and she's hoping it will be published soon.

**This might be a very simple question, but what mutations did you find? Were they all seemingly negative mutations, or did some of them seem positive? Could you tell at all, or was it simply that the DNA didn't match?**

**Thank you for your hard work!**

**Thank you!**

[Zerosen\\_Oni](#)

There are algorithms we can use to predict whether a mutation will be harmful or neutral (they don't tend to predict beneficial mutations), and we ran our data through those algorithms. Most were neutral, but we did find some that were predicted to be harmful.

Thanks for your question!

**Mollie! I have read every single one of your MIT Admissions blog posts, and I think you're an amazing writer and person! You're honestly a personal role model to me; the passion with which you research and live your life has been inspiring to me. My questions: can your findings be applied for some form of therapy to treat mutations early on to avoid perpetuating them? What kinds of effects, both negative and positive, do these mutations specifically have?**

[qscgt12](#)

Thanks for the kind words! It means a lot to an old, world-weary postdoc.

Unfortunately, I think our work really points to the idea that mutation is something that's happening across your brain every day.

Many of the mutations we observed were C>T mutations, which often happen when a methylated C becomes deaminated to a U, which looks like a T upon sequencing. This implies that mutation is just a consequence of the normal chemistry of DNA, and there's probably no way around it. On one hand, that's great! Mutations are the grist for the mill of evolution. On the other hand, that's terrible! All life, and your entire brain, is inevitably sliding toward death and decay.

- **Are there signs that the neurons are mutating themselves with nucleases of some sort?**
- **Did you compare central and peripheral nervous system? Any difference?**
- **What other tissues did you compare to? Is this definitely just neurons?**

[dspeyer](#)

No evidence of a specific nuclease...the mutations seemed to be mostly the result of random base degradation. For this study, we only looked at CNS; cerebral cortical excitatory neurons to be exact. We compared the neurons to either heart or liver DNA in bulk, so any single-cell mutations in these organs would not have been detected.

**Have you checked to see if any neurons are aneuploid?**

[bjornostman](#)

Another great paper from our group looked into this (<http://www.ncbi.nlm.nih.gov/pubmed/25159146>) and found the rates of aneuploidy to be very low.

**Congratulations on your discovery, just a few questions.**

**In the abstract it was said that the three brains you studied were healthy brains from people who died in an accident. What were the ages of the individuals and did the difference in age show a difference in mutations?**

**Also in your opinion what would be the best way for a non professional to keep up with new findings such as this**

**Thank you for your time and once again congratulations.**

[Tahetal](#)

Thanks! The three individuals were 15, 17, and 42 yrs old. We did not see any differences between them in terms of the number of mutations, suggesting either that the number remains stable during life, or that we will only see such a trend after looking at many individuals, due to inter-individual variability.

Gotta give a shout-out to [/r/Science](#) as a great place to hear about cool new research! PBS NOVA, NPR Science Friday, and the New York Times Science section also do a great job with this.

**Could this process be beneficial? Like in the immune system where the mutation in the variable parts of the IG. genes leads to the ability of B and T cells to recognize pathogens. Of course you would need some kind of positive and/or negative selection mechanism for neurons too.**

[Lecsicon](#)

The mutations we found seemed to be too random to be directed by any process, so this is unlikely.

**Is there any possibility that some mutations are memory carriers? I mean, once upon a time there was the notion of *gene* but noone knew what exactly it was until DNA was discovered. Is there a chance that at least part of memory is in fact typed in DNA? Since these cells don't multiply it is a convenient thought...**

[marathon16](#)

We did not find any evidence of these mutations being involved in memory, and there is no evidence that we know of that somatic mutations are directly induced by cells in the brain to encode memory.

**What is the likelihood that one day a neuron mutation or group of neuron mutations will give us an awesome superpower?**

[SkywayTraffic](#)

We are very optimistic.

**Hi there, that's quite an introduction. Any chance you can explain it to us as if we were five?**

[Super\\_King85](#)

One of us has an actual five-year old, so here goes:

Every cell has an instruction book with all the plans it needs to do it's job, called DNA. Every time that cell divides to make more cells, like when we grow, it has to copy this long set of plans so each new cell has a copy. Sometimes, there are mistakes during this copying, like a game of telephone. Sometimes, just from reading the instruction book the words get smudged or pages get ripped. We call these mistakes somatic mutations, and we studied these mutations in this paper.

**Since neurons are most exposed to mutation due to its lifelong survival as you've mentioned, how does it cope with the relatively rate of mutation and function efficiently ? Is it possible to say whether or not there has been an increase if any in the mutations caused these days due to our over exposure to physical and chemical mutagens as compared to the previous generations ?**

[ballmagneto](#)

That would be pretty difficult to test, since we rely on having well-preserved frozen brain tissue to sort neurons with high-quality DNA -- I think it would be tough to get comparatively preserved tissue from 20th/19th/18th-century brains. And the brains that are preserved from back then tend to be pretty precious, and only from wealthy or important people.

- 1. Have you consider examining neurons of human in different age. From infant to 100-year-old? I know it sounds terrible.**
- 2. Is it possible that these mutations result in differences in human behavior?**

[SirYoggi](#)

1. Yes, definitely! We looked at a 15-year-old, a 17-year-old, and a 42-year-old in our paper, but we are very interested in looking at brains from people of different ages in a more systematic way. We are very lucky that we have access at Harvard to a few fantastic brain banks that collect brains from Alzheimer's patients and normal aged controls. (PSA: Brain donation is awesome and so appreciated!)
2. It's possible, although we didn't examine this in the present study.

**Hey guys,**

**Thanks for doing this AMA.**

**I was wondering what you thought the implications of your research might be in terms of the cell of origin of glioma.**

**Inder Verma's group has shown with mouse models and lineage tracing that glioma can arise from mutations targeted to neurons such as P53 and PTEN deletion.**

<https://www.sciencemag.org/content/338/6110/1080.figures-only>

**I would love to hear your thoughts on neurons potentially serving as a cell of origin for glioma given your finding that mutations in neurons are located to primarily non-coding areas of the genome.**

**Thanks again for your time.**

[heaventreeofstars](#)

We are for sure not cancer experts, but that caveat aside, our work does at least establish a possible mechanism by which neurons could generate cancer cells. However, if we think of the path of least resistance to forming a tumor, it is probably more likely that a mitotically active cell like a glial cell becomes transformed than a post-mitotic neuron, since for the neuron you would need that many more mutations just to enter the cell cycle.

**How do you filter out which mutations actually DO something or have a real effect. My understanding that it is certainly possible for a mutation to alter the amino acid sequence on a protein, but on the physiological level, the mutation has no real deleterious effect on protein activity or folding.**

[heyheyravens](#)

There are several algorithms that predict the effect of a mutation on a protein, including PROVEAN, SIFT, Polyphen-2, and others. No single algorithm is perfectly accurate, so it's common to run a candidate mutation through several of these algorithms to decide whether it might be harmful to the protein.

**Will you be publishing the underlying sequences?**

[dakami](#)

Sequencing data have been deposited in the NCBI SRA under accession numbers SRP041470 and SRP061939. Enjoy!

[removed]

[\[deleted\]](#)

We promise darkzero26-50 will be ready soon my lord.

**How much lineage tracing has your group done so far? Any specific areas you plan to search?**

[antiward](#)

Not as much as our boss would like!

We are currently collecting tissue from brain banks, but we're limited by what's available. Everybody wants a piece of famous areas, like Broca's area or motor cortex, so we want to find something with nice clear anatomy that isn't likely to be already taken by some other lab.

**Do neurons from some brain regions (e.g. prefrontal cortex, hippocampus) have more mutations than neurons from other brain regions?**

**How does the rate of neuronal mutations change with age?**

**Do people who learn faster (and whose brains undergo higher amounts of LTP/learning) accumulate higher rates of DNA mutations?**

[inquilinekea](#)

So far we've only looked at neurons from prefrontal cortex, but we plan to look at neurons from other cortical areas and from hippocampus in the next few months.

We're definitely interested in the aging question as well, and have acquired brains from a range of ages to investigate.

**Hello. First of all I am so grateful to you both and to everyone involved with this research. Thank you.**

**I am not a scientist and do not have a neuroscience background-here are my questions:**

- 1. Is there a point where the human body will try to destroy or replace the cells which have mutated or once they are there they, well, they are there?**
- 2. Do the mutated cells function the same as the other cells in that family/area? Is there or has there every been a case where the mutated cells produced a catastrophic impact?**

**Thanks in advance for addressing a layperson's questions (hope they aren't too silly) and greetings yh.**

[gingermonkey1](#)

1. It's possible that a mutation could cause a cell to undergo programmed cell death. Actually, that's what we would prefer would happen if a mutation affected a cell so much that it was unable to function. But most of the mutations we observed are probably not harmful or helpful -- they are just in non-coding regions of the genome, where they are probably not affecting the cell's function in any way, so the cell isn't motivated to fix them.
2. Since we were looking at postmortem brain tissue, we don't know how the cells we sequenced were functioning in the brain. Some of them had mutations that would cause disease (if they were present in all the cells in a person's body), so we would suspect that they weren't functioning optimally, but we don't know for sure.

**Do they mutate the same way (or at least similar) on the brains of different people, or are these mutations random and unpredictable?**

[TiagoTiagoT](#)

The three individuals whose neurons we sequenced had very similar patterns of mutations. We would suspect that the patterns of mutation that we uncovered are generally applicable, but we will need to sequence neurons from more people to be certain.

Just to be clear, though, we found *patterns* of mutation that were similar across neurons and between people, but the mutations themselves are not the same. There are clear patterns, but the genome is huge, and the number of mutations is small.

**Have similar mutations been detected anywhere else in the body?**

[TiagoTiagoT](#)

Yes, definitely. In our paper, we identified mutations in the brain that we went on to find in other organs, including heart, lung, pancreas, and liver.

There are also some other recent papers that have looked at the rates of mutation in normal [kidney cells](#) and [skin cells](#), and I suspect there will be a lot more papers like this in the near future.

**Okay so by my very rough math: 2% of a 3 billion base pair genome is coding and there are 1500 errors/cell, 1.4% of which are in coding this is 21 coding errors per cell 86 billion human neurons so this is 21x86=1806 billion SNVs coding regions only have 60 million bps in them so this is...roughly 30,000 oversampling each coding base pair in the genome is mutated in 30,000 cells this means that each possible amino acid substitution is sampled roughly 1000 times by different cells all over the brain**

**Do you agree with this math? Can we find these 1000 cells through some sort of probe and then record from them? Want to collaborate? PM me. I am interested in how ion channel properties affect coding properties.**

[lobocop](#)

No sure how we could find these cells prospectively before sequencing the DNA, but agreed on the point that every gene in the genome is mutated many times over in the body, a very jarring thought!

**Do you take into account the role of adult neurogenesis on these mutations? Can you control for/differentiate which neurons developed embryologically and which came later, and if so are you able to see any relation between this and the amount of somatic mutations?**

[aupeters](#)

The specific neurons that we studied for this paper came from the adult prefrontal cortex, where there is no neurogenesis under normal circumstances, so we are confident that they were born during embryonic development.

We are really interested in how somatic mutation might be different in regions, such as the dentate gyrus of the hippocampus, where there is ongoing neurogenesis in adults. We have an awesome MD/PhD student on the case, so stay tuned.

**Thank you so much for the work that you do. As a researcher working in a bFTD lab, I'm particularly interested in the clinical diagnosis of dementia. Has any of your work indicated a relationship between somatic mutations and demented behavior?**

Thanks.

[barnburning](#)

Dementia isn't one that we've looked at, actually -- that's a really interesting idea.

If I had to predict, I'd say that where there are germline mutations, there are somatic mutations that haven't been identified yet. One bonus of somatic mutation as a disease driver is that you can get mutations in genes where a germline null would be incompatible with life.

**Are you afraid that a bunch of inmates will out-science you?**

[moatmoatmoat](#)

Nah. We both went to MIT (Mollie for undergrad, Mike for grad school).

**Hi, what kind of mutations are they? Are there CpG to TpG mutations from methylation and spontaneous deamination?**

**I don't seem to have access to the full article. Thanks :)**

[samsoniteINDEED](#)

Yes, indeed! Actually, that's what they mostly are. 60-70% of the SNVs are C>T, and are significantly more likely to be in a CpG dinucleotide context than any other (although CpH sites are also more likely to mutate).

Sorry you can't access the paper -- there's actually a whole supplemental figure about this issue.

Hello!

**Thanks for the AMA, You mentioned you sequenced postmortem human brains, so I was**

**wondering hypothetically if you were given access to a live fetus neurons and watch it develop and study them would u tag them before or after the 20 week time period?**

**What might you hope to observe if given that opportunity?**

[ThatDCguy69](#)

There's been some really beautiful and fundamental developmental biology work done in fetal human brain, but ethically and practically, we can't keep it alive and in good shape longer than about 3 days.

Neurogenesis occurs in humans between about week 7 and week 20, so we would probably get more scientific work out of an earlier brain than a later one.

Fetal tissue research is incredibly important to developmental biologists. We are so grateful to the people who donate fetal tissue to labs all over the US and the world, and we do our best to honor your donations with our work.