Science AMA Series: I am Dr. Nikolay Dokholyan, professor at the University of North Carolina School of Medicine in Chapel Hill, N.C., here to talk about a major development toward understanding ALS an

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Abstract

Hi Reddit, As the Michael Hooker Distinguished Professor of Biochemistry and Biophysics at the UNC School of Medicine, I study the causes of human diseases such as cystic fibrosis and amyotrophic lateral sclerosis (ALS). Every day, an average of 15 people are newly diagnosed with ALS. That's more than 5,600 people per year. Annually, ALS, also known as Lou Gehrig's disease, is responsible for two deaths per 100,000 people. Along with my colleagues, I recently completed some research on ALS that could lead to significant developments in how we treat the disease. In my lab, we approach research very differently than many other labs. We use integrated strategies to replicate molecular structural modeling. This way, when we analyze the structure and dynamics of biological molecules, they are at consistent time scales to actual biological systems. This is also how we approached our ALS research. Although there has been a significant amount of research on ALS, the exact form of the aggregated protein responsible for killing neurons has been hard to identify – and even harder to study. To crack the mystery, our team used a combination of computational modeling and experiments in live cells. We spent two years developing a custom algorithm to determine the molecules' structure, which is an outstanding feat. Next, we spent several more years developing methods to test the trimers' effect on motor neuron-like cells. The results of our study, published in Proceedings of the National Academy of Sciences, show the first definitive evidence that these protein clumps are indeed toxic to the type of neurons that die in patients with ALS. Our findings raise a lot of questions about what this could mean for halting the progression of the disease and, eventually, developing its treatment. I will be back at 1 pm EST (10 am PST, 6 pm UTC) to answer your questions, Ask me anything! Edit: Thank you for all the great questions! I'm signing off!

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REDDIT

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DR_DOKHOLYAN R/SCIENCE

Hi Reddit,
As the Michael Hooker Distinguished Professor of Biochemistry and Biophysics at the UNC School of Medicine, I study the causes of human diseases such as cystic fibrosis and amyotrophic lateral sclerosis (ALS).
Every day, an average of 15 people are newly diagnosed with ALS. That's more than 5,600 people per year. Annually, ALS, also known as Lou Gehrig's disease, is responsible for two deaths per 100,000 people. Along with my colleagues, I recently completed some research on ALS that could lead to significant developments in how we treat the disease.
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This is also how we approached our ALS research. Although there has been a significant amount of research on ALS, the exact form of the aggregated protein responsible for killing neurons has been hard to identify – and even harder to study.
To crack the mystery, our team used a combination of computational modeling and experiments in live cells. We spent two years developing a custom algorithm to determine the molecules' structure, which is an outstanding feat. Next, we spent several more years developing methods to test the trimers' effect on motor neuron-like cells.
The results of our study, published in Proceedings of the National Academy of Sciences, show the first definitive evidence that these protein clumps are indeed toxic to the type of neurons that die in patients with ALS. Our findings raise a lot of questions about what this could mean for halting the progression of the disease and, eventually, developing its treatment.
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I recently recall reading a study showing in a much higher proportion of ALS was of genetic etiology than previously thought, i.e. only those related to the SOD cluster. What are your thoughts on that?

Also, thoughts on the Oregon state work?

And finally, how relevant is the mouse model for this particular disease?

StopTheMineshaftGap

ALS like many other diseases is rather an umbrella name for a set of symptoms and is a collection of many rare diseases of potentially unrelated molecular origins. The way how disease is diagnosed is by a set of symptoms, which uniformly show muscle atrophy and motorneuron death. However, there can be many reasons why motoneurons die, i.e. there can be multiple, potentially unrelated abnormalities in motoneurons that lead to their death. SOD1 is one of the genetically liked to FALS proteins. There

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are many others, but at this point there is no proof that these other proteins do or do not have common pathways that lead to cell death. Hence, making ALS a collection of many rare diseases. From ethical perspective I do not feel it is only beneficial to pursue biggest offenders, like C9OPF72 or TDP43. Having said that, the disease etiology does have similarities between many of the "offenders" and hence understanding what is going on with SOD1-linked ALS may allow us to grasp what is happening with etiologies of other ALS types.

Do you believe treatment will ever be able to reverse the damage done or will it be a preventive measure to halt the disease?

LAcycling

Absolutely! I truly believe we will find it. I would not have spent my last 13 years on this subject if I did not believe in finding the cure. Having said that, I firmly believe that in order to find cure we need to uncover the origin of the disease: what is actually killing cells and why, so we can target the root of the problem. What makes ALS particularly difficult is the fact that it is a collection of many rare diseases and we need to study it case by case. Hence, we work on one particular case of SOD1-associated ALS.

Thank you so much for doing the work that you do and for doing this AMA.

I was wondering if you could comment on the possible connection between brain trauma and ALS. I've read that there are higher incidences of diagnosis among combat vets and athletes (particularly football players), but my understanding is that ALS isn't really caused by something like that. I've read those diagnoses may be something slightly different from ALS.

My dad died from ALS 2 1/2 years ago. He had a brain tumor removed three years before his diagnosis. I was just always curious if there was a chance the two were related. Thank you.

finegirlbrandy

This is a very interesting question. SOD1 plays role in sporadic ALS as well as in familial ALS. I will try to answer from SOD1 perspective. When we started studying how and why SOD1 aggregates we were puzzled by exceptional stability of this molecule, yet its destabilization was required for aggregation. None of the familial mutations can by themselves explain SOD1 aggregation. This puzzle led us to a hypothesis in 2007-2008 that something happens to this molecules after it has been synthesized in our cells, namely it becomes post-translationally modified. To prove this hypothesis, yours truly collected his blood and isolated SOD1. That SOD1 molecule was indeed modified: it featured phosphorylation and glutathionylation. We spent next few years to prove that glutathionylaiton increases SOD1 dimer dissociation 1000x fold (Redler, R. L., Wilcox, K. C., Proctor, E. A., Fee, L., Caplow, M., and Dokholyan, N. V. "Glutathionylation at cys 111 triggers dissociation of wild type and fals mutant SOD1 dimers", Biochemistry, 50:7057-7066, (2011)). Glutathione addition happens during oxidative stress in the cell. Glutathione protects free cysteines on proteins, and it does that to SOD1 as well. However, SOD1 dimer stability is strongly impacted by glutathione, which, especially on the background of genetic mutations, promotes population of monomers, and further aggregates. Hence, the oxidative stress may be environmental trigger for ALS and patients who carry FALS mutations are more susceptible to the oxidative stress.

There was a recent study in the news that show a remarkable progress in mouse models. They devised a delivery method for Copper-ATSM to the brain and they claim that this disease can be changed from lethal to a chronic disease. Is this true?

Link: http://www.ibtimes.co.uk/als-shockingly-successful-copper-atsm-mice-trials-show-first-signs-prolonging-life-1540816

chillinewman

This is indeed a great work from Joseph Beckman lab. His story is indeed consistent with what we know about SOD1 aggregation: back in 2004 we showed that for SOD1 to aggregate it must dissociate, lose its metals and then form aggregates. What Beckman lab has done is to interfere with the loss of metal step and it showed beneficial effects in mice. I hope their approach will be successful in humans.

What is the consensus among experts on Stephen Hawking's survival to date? Has any attempt ever been made to reach out to him for current or posthumous study by the medical community?

Terminusbbq

Great question! Exactly my point that ALS is not one disease. It is a collection of rare diseases and Stephen Hawking's case is particularly interesting because of unusually long duration. Maybe in the future when we learn how to classify all these types of ALS, his form of ALS will have its own name.

This is very interesting to me as someone with MS, which has many similarities, can you talk about how your research might be applied more broadly perhaps to understanding more about MS or other diseases that have commonalities?

HeythereHighthere

Unfortunately, I am not aware of links between MS and ALS. What is known is that it is highly rare for people with MS to be diagnosed with ALS.

I'm pretty ignorant on the subject and I'm sure I'm not alone. What are one or two major things we should understand about it and how to be helpful

h_word

Thank you. Neurodegenerative diseases feature protein aggregation, but it is unknown whether protein aggregation is the cause. We have demonstrated that aggregation process does produce toxic particles that can kill motoneurons. Why this finding is important is because understanding what kills cells may help us target those culprits with drugs. Not only we identified the culprits, we learned its structure, which is required for structure-based drug discovery efforts, currently going on in our laboratory.

What advice would you have for someone with a background in bench science (molecular biology) looking to transition to a more computational approach? What do you consider the essential skills?

15blinks

Actually I am agnostic about the tools. My master's thesis was on pure theory (Physics) then I was involved in mostly computational research, when I joined UNC in 2002, I needed to test my computational predictions, so we started doing experiments. A few years ago, we wanted to test our predictions in cells, so we started doing cellular biology experiments. One of our projects now is to discover a biomarker and we collaborate with the doctors who work directly with patience, which allows

us to have a connection to clinical studies.

As as scientist I am interested in a problem and I use tools that around me to solve these problems. If these tools do not exist, we try to develop such tools. With this approach, we remain focused on the big picture: the problem at hand, rather than stop due to limitations in the approaches.

My most essential skill in science is curiosity. I cannot stop asking questions "why?" and that is driving my research. Of course there are other skills that one need to master: learn to be pragmatic and know the limitations of the studies, yet never give up. Education is also an important asset.

Hi Dr. Dokholyan,

From what I have learned in medical school most neurodegenerative diseases are either due to aggregates predominantly of ubiquitinated tau or a-synuclein. ALS, however, seems to be caused by aggregates of many different proteins. As far as you can tell is there any reason for this difference between ALS and all the other neurodegenerative diseases? Or is it a simplification to say the aggregate in alzheimer's is only tau and it actually has many proteins as well?

Also, do any other organ systems have protein-aggregate diseases like the CNS does? What makes neurons so vulnerable to accumulating toxic protein? Is it their long life-span?

Thanks!

SerPounce218

As I mentioned in several replies, ALS is a collection of rare diseases, featuring a similar process - aggregation. So it is not surprising that people observe different players in different types of ALS.

Protein aggregation may also be beneficial, e.g. by tanning our skin and protecting from UV radiation.

Protein aggregation is also associated with may other diseases, such as diabetes, hemodialysis-associated amyloidosis, and familial amyloid cardiomyopathy. Brain is not the only organ that can be affected by protein aggregation.

Looking back on the past few years, is there anything specific that would have made your research progress faster? More manpower? More money? Better communication with fellow researchers?

And thanks for doing the AMA!

thelastrhino

ALS is a rare disease, which makes it harder to raise money to study this disease. Even more challenging from the financial perspective to endeavor into drug discovery, due to risks associated with the process and pharma companies focus on diseases that affect larger groups of people. So any support helps.

University of North Carolina has established a fund that would benefit ALS research at UNC. The advantage of this fund is that money go directly to the laboratory without any administrative overhead. If you wish to help in our effort for drug discovery, please use this link: Neurodegenerative Diseases Research Fund (345845)

http://giving.unc.edu/gift/custom/index.htm?fndpic=345845&p=medf

My father has ALS and I've been glad to see that there is a lot of forward momentum towards figuring it out. I don't really have any questions about it that haven't already been asked, but on a personal level, thank you. Its you and people like you that have given us a little more hope.

Given it's an AMA I hope this is appropriate.

smile-with-me

Thank you for your support.

Did donations from the Ice Bucket Challenge help fund projects in your lab?

shuzy

Sadly no :) However, University of North Carolina has established a fund that would benefit ALS research at UNC. The advantage of this fund is that money go directly to the laboratory without any administrative overhead. If you wish to help in our effort for drug discovery, please use this link: Neurodegenerative Diseases Research Fund (345845) http://giving.unc.edu/gift/custom/index.htm?fndpic=345845&p=medf

Can you explain a little more the significance of the study and how it could help us find a cure? I lost my father to ALS in 2010 and I've been trying to help people fight this disease since.

I_DILL_E

I am sorry to hear about your father. Why we want to understand the etiology of the disease is because we want to interfere with this aberrant pathway. In our example, we are pursuing double-edged strategy for drug discovery. We found that for SOD1 to aggregate it must dissociate, which is promoted by glutathionylation, lose metals, undergo conformational change and form toxic trimers, and then further aggregate. We are targeting both the first step (dimer dissociation) by finding small molecules that would stabilize SOD1 in its native functional form and the trimer interface to prevent trimer from formation. It is too early to talk about our drug discovery efforts, but I would like to emphasize that 13 years of work directed towards understanding of the SOD1 aggregation pathway is critical to our current drug discovery efforts.

There are obviously many forms of motor neuron disease, and even many forms of ALS itself. How do researchers tackle the various forms (e.g. familial), onsets (e.g. bulbar onset), and comorbidities (e.g. FTD) of ALS and is there anything about your research that suggests these protein structures are the culprit in all forms of ALS and its associated comorbidities?

robbiedenali

That is a great question! Yes, this is a problem in the field: doctors diagnose the disease after many (elaborate) tests that are mostly based on symptom presentations. Those different cases may be results of distinct and quite different disease etiologies associated with potentially completely unrelated proteins in motoneurons. Since there is no therapy at the moment, from the treatment perspective these differences may not be very critical. The doctors are helping with the symptoms and developing strategies for end-of-life care. To make a difference in developing therapies, we need to start distinguishing these diseases at the molecular level and aberrant pathways. Sadly, at the moment, we do not have even biomarkers that would definitively states that a patient has ALS.

ALS research is something I hold near and dear to my heart. I lost my father in 2012 to ALS. He was only 47 years old, and had been diagnosed when he was just 44 years old. I want to know what kind of timeline you think your findings may eventually create, in terms of developing treatment? In other words: realistically, how close do you think you are to developing treatment/a cure?

Also, I want to thank you, and everyone else, who is involved with researching and fighting this disease. Frankly, I would never wish it upon my worst enemy. It truly is hell watching someone be a prisoner in his/her own body.

kittycat_

I am so sorry about your father. Thank you for your support.

I can mention where we are: 13 years ago I would not have even dreamt of searching for drugs for ALS based on our research because there were so many puzzles about SOD1. Now, we are actively searching for drugs and, while I should abstain from any comment on the effort (to avoid any false hopes), I am personally optimistic.

In the field there is a significant drug discovery effort going on and I am sure several independent approaches for ALS treatment will start to emerge soon.

Two people I know have died due to ALS.

First is an electrician, aged 65, diagnosed with ALS at 63.

Second is a commercial airline pilot, after 15 years spending time inside cockpit, was diagnosed with ALS and 3 years later passed away.

Question: Does their profession (spending long time exposed to electrical and electronic devices) has anything to do with ALS? Any research on any links of chemical exposure to ALS?

violin_beginner

What we have learned from SOD1-associated ALS is that just familial mutations may not be sufficient to promote protein aggregation. We found that oxidative stress is a major trigger of the disease. Having said that I would not rush to assumptions that these professions are dangerous. Simply, there are no studies I am aware of that are showing any relationship between profession and the disease.

My mother died of ALS in 88 and since then the area we live, there have been at least 10 other deaths from ALS. Are clusters rare and should something be looked into about this. We live SouthEast of Montreal.

FatInTheMiddle60

I believe that there are environmental triggers that may promote the disease.

If someone wants to donate to the cause, what is your opinion on the best place for it to go?

Stoshels

Professional associations like MDA and ALSA are great organizations that promote ALS research. University of North Carolina has established a fund that would benefit ALS research at UNC. The advantage of this fund is that money go directly to the laboratory without any administrative overhead.

If you wish to help in our effort for drug discovery, please use this link:

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Thank you for your work and for your time with us today. I have known two people that have ALS. Both had mononucleosis as a teenager. I've often wondered, is there a correlation?

salinger007

I am sorry about your friends. I am not aware of the connection between the disease, but I would not rule out such a connection.

Hello Dr. Dokholyan,

Earlier this year I attended a lecture with the geneticist that found the C9orf72 link to ALS. He suggested that most sporadic ALS may be familial ALS that we just haven't found the mutations for. I asked another ALS researcher about it, who had the opposite viewpoint.

Based on your own experience in the field, do you have an opinion or speculation on it?

slthomp2

ALS is a complex disease with potentially many distinct origins. Depending on what type of the disease a scientist is pursuing she/he maybe biased by their studies. C9ORF72 is emerging as a major player in ALS, but it may have a distinct molecular etiology than SOD1-associated ALS with non-overlapping molecular pathways leading to motorneuron death.

Hi there! Thanks for doing this AMA!

It remains unknown if aggregates are the cause of or result of the disease, and while there has been some promising results preventing the onset or progression of Alzheimer's by preventing aggregates, there are plenty of associated mutations that are related to underlying cellular mechanisms, such as the unfolded protein response, endocytic pathways, fast axonal transport, and transcriptional control.

Do you think approaches targeting these other avenues of dysfunction as therapeutic targets may be more fruitful than targeting aggregates themselves?

Izawwlgood

When cell is dying, there are many processes that activated in the cell and in the tissue, such as unfolded protein response, inflammation, transport. Targeting those processes may be of a huge benefit in terms of alleviation of symptoms and prolonging life. We are targeting currently one of these pathways in hope to prolong cell life. However, to find a cure, I believe we need to find a true culprit that triggers activation of these aberrant pathways.

I just wanted to say that I appreciate all the work you are doing! My father was diagnosed 3 years ago and luckily we've been fortunate enough that the disease has only affected his shoulders and arms.

From his most recent tests from a few weeks ago, he still has no signs of ALS in his legs and his breathing is above average for a normal 60 year old male.

We just take things day by day but please keep up the work. We never thought this disease would hit our family but yet, here we are.

He is about to enter a clinical trial using some sort of viral therapy. Since his ALS has only progressed so far, he is a candidate for the trial.

PIG20

I am sorry to hear about your father. I wish him success with the treatment.

Is protein aggregation the cause or just an effect of ALS?

PureVegetableOil

Great question. We do not know yet. We know that SOD1 trimer is toxic, but we do not know whether it is the cause of ALS.

If we discovered a way to eliminate those harmful protein clumps, is there any chance motor function would begin to improve, or would it simply halt the decline?

Kage520

If we prevent toxic clumps from forming while motorneuron is still alive, then we should not expect symptom presentation. However, if symptoms are present, that means that motoneurons are already dead and the treatment would only protect surviving motoneurons and hence prevent from future decline.

I lost my grandmother to ALS when I was younger. The hardest part for our family was slowly watching her own body system killing herself and there wasn't a damned thing we could do to stop it. It hit my grandfather the most as he is a member of the national academy and use his wealth of knowledge to do everything he could try to stop the progress of the disease.

My question is how can one take your research and knowledge to come up with a targeted approach in halting the progress of this disease? Additionally, how has your lab made progress in determining how people acquire ALS? Does it appear to be more environmental or genetically?

The latter question has always been in the back of my mind as I fear that myself or other family members will go through the same horrible process that my grandmother had to experience.

I would really appreciate any information. Thanks

tanandblack

I am sorry to hear about your grandmother. I have addressed some of your questions in previous questions. I think both genetics and environmental factors contribute to disease. What make ALS even more complicated is that there are gene modifiers that make this disease manifest itself differently in different patients.

Could the research you're doing per ALS be applied to other similar genetic illnesses such as Spinal Muscular Atrophy (SMA)

pantaleano

We are trying to delineate the molecular etiology of the disease. If we succeed, this approach will serve as a framework to approach other protein misfolding diseases.

You speak of 'protein clumps' that are toxic to neurons being central to the disease. The obvious question is where this protein comes from? I read something about a neurotoxin called BMAA that concentrates in seafood may help explain clusters of Lou Gehrig's disease. (they found increased occurrence in ALS in areas where people ate lots of seafood source

puntloos

SOD1 is present ubiquitously in our brains and it functions to protect our neurons from oxidative stress. At some point this protein start misbehaving and becomes toxic. When it does it is present in a clump of three halves of SOD1 molecules.

BMAA story is fascinating and emphases two points that I would like to make: (1) ALS is a collection of multiple rare diseases of diverse origin, and (2) environmental factors are as important as genetics to the etiology of the disease.

I've got a biology degree but we spent very little time in university on computational study. What is the process that you go through to create your algorithms? What do you find important and what information do you find reasonable to discard?

cynicalfly

Great question! Computers for many people are mysterious machines that do stuff. This is actually true: they do what you ask them, but it is you who is asking them questions and telling them how to answer them. Computers just take the hard work computing things that otherwise you would do on a piece of paper. So, all we did was take carefully designed wet lab experimental data and asked computer to show all possibilities of a protein structure to be in agreement with what we observe experimentally. When we got the answer, we validated these structures in further experimental studies. The moral of the story: computers are dummies, they do not think. They just help you to avoid many routine steps in your thinking process.

As an organic chemist, I've rarely found computations to be predictive, but rather descriptive. Working in a biological setting, would you say that your models tend to predict things you wouldn't have expected and then later support with experimental data, or is it more likely that you get an interesting result from your bench work, and utilize modeling to understand what's going on?

thebrew221

Great question! I am also skeptical of any work that I do, whether it is computational or experimental. We always have to prove that something that we do with one approach is not an artifact of that approach. In this story, we have validated the structure by designing new mutations that would stabilize or destabilize the trimer and it worked in all 7 cases. Is it enough, I do not know, but it is a great start and the study reveals an important message that small oligomers are toxic.

So a while back I watched this documentary about ALS and this couple both got the desease. They werd asked if they knew anything out of the ordinary they botth came in contact with, and they pointed out that they slept next to the same lead plate. But not real effort was put info researching the thing. I told my parents that was because lead is a well known element and the research would propably fail.

Does anyone know if this was the case?

IanMu

that is what we are tying to answer. At this point it is unclear but we are getting clues.

Hello Dr Dokholyan.

When you mention integrated strategies to replicate molecular structural modeling, you mean your Molecules in Action? There are some other molecular mechanics modeling labs and soft, what's the main difference?

You said that results of your study could eventually help to develop treatment. Does scientists have at least the approximate idea how it should work?

Also, if I got it right, you are from Russia? Did you got your university education in Russia, or you moved to USA before it?

Ofcyouare

In terms of how treatment should work: if we know molecular pathways leading to motorneuron death, we can interfere with these steps with the goal to rescue cells. We are currently targeting SOD1 dimer stability and trimer from forming.

I was born in Tbilisi, Georgia, got my MS in Physics from the Moscow Institute of Physics and Technology. I came to Boston University to get my PhD in physics, but refocused on problems in biophysics while in Boston.

Which "protein clumps" have you found to be toxic? Mislocalized TDP-43, dipeptide repeat proteins, phospho-TDP?

Do your results tie in at all to the developing "plugged nuclear pore"/dysregulated nucleo-cytoplasmic transport story that is recently developing in the ALS field?

schlummy

We found SOD1 to form toxic trimers. What we are trying to understand now is how these toxic trimers lead to cell death.

Hello Dr. Nikolay Dokholyan

What is your opinion on the ALS Ice Bucket Challenge? Do you believe the cause was good, or that it was a publicity stunt?

Doctor_Red

I think it was an incredible idea that raised awareness of this rare disease among us. Here is our contribution :) https://youtu.be/RtaPIAbVjgQ

I've heard that they younger you are when diagnosed, the longer you are likely to live with the disease. Is that true? Hawking got it as a young man and is still alive whereas my uncle got it at 65 and died within a few years.

gperlman

I have not heard of such studies. The only reason I can think of that can be true is because younger people tend to have more muscle mass, so they have more to lose. This is a speculation that may not be true at all.

I'm not sure how to phrase this question, so please bear with me some.

My family has an extensive neurological disease history, my grandmother passed away from ALS 5 years ago. (She actually did travel to Chapel Hill since we are in NC as well) Her mother was diagnosed with late onset Parkinson's Disease decades before. My grandmother's brother has something that no one is willing to diagnose. He cannot speak at all anymore. He can eat/walk, but just barely. He's been this way for ~10 years, though it has gotten worse over the course of time. My brother has epilepsy (semi-unrelated), but the neurological issues in my family are extensive.

My mother and grandmother had some genetics testing done when she was first diagnosed. The results said the disease shouldn't be hereditary. However, with this much neurological disease in my family's history--it's a little terrifying. Have you noticed genetic links passed between families with ALS? Is it possible that Parkinson's was more well known in the past and could have been a misdiagnosis for ALS?

I've found that familial ALS is supposed to be rare, but would it really be obvious on a test? Would you recommend someone from a second generation (myself or my siblings) get genetics testing done as well? My siblings and I are scared of having children or developing these diseases ourselves, especially since we weren't there when the genetics tests were done originally to ask questions, etc.

livelaughdesign

I am a big proponent of knowing your genetic markup but it is always a personal choice to know about them. If you are interested to know there are companies like 23andme.com that can profile your genome.

Dear Dr. Dokholyan, Thanks for having a reddit AMA on ALS - we definitely need more of these discourses. My input is actually two-fold, the first part of which is a question: Are you planning to use a similar methodology you used in your PNAS paper to look more closely at abnormal Dipeptide Repeat Proteins (DPR) arising from RAN translation of the G4C2 repeat expansions. I believe although recent papers have shown the importance of DPRs in neurotoxicity, the exact nature of how they exert such effects are unknown?

The second part of my input is drawing attention to Kevin Gosnell's extraordinary response and testament of strength through the formation of ALS one organization. He is trying to bridge the gap between patients, affected families, and doctors by his amazing resolve and through this effort. I had the opportunity to talk to Kevin a couple of weeks ago, and his strength and resolve in the face of aggressive ALS is incredible, and outstanding. I want to draw attention to this amazing person and his fight against ALS http://www.alsone.org/

Thanks again.

budhaChowdhury

thank you. For now we are focusing on SOD1-associated ALS.

Hello Dr.

I suffer from Ms. I also am a neuroscience major but I am still completing lower level courses at the moment. I am curious to know if there are any links between ALS and MS?

Thank you for your time

Keemami

Sorry about the disease. I am not aware of any link between MS and ALS, except people with MS have lower chances to develop ALS.

Hi! Thanks for doing this AMA. I did a rotation in an ALS lab out at Wake Forest University in 2011 when I was starting my PhD. I think your work is incredibly interesting. Do you think these structural insights will give you the tools you need to disrupt the trimer formation of the mutated SOD1? It seems as though you have identified destabilizing mutations and validated them with genetic mutants, do you plan to investigate siRNA constructs/any intervention method in mouse models of ALS?

spare0h

Disrupting trimer formation is one of our strategies. thank you

Always nice to see a Tarheel on Reddit.

What info, if any, do we have on why Stephen Hawking has lived to the age of 70 when so many people have died within years of diagnosis? Also, what steps are or do you think should be taken to allow researchers to revisit this issue after his lifetime?

EvaUnit01

Thank you.

ALS represents multiple rare diseases with potentially distinct etiologies. Stephen Hawking has a form of ALS, which is rather uncommon.

Hi Dr. Nik! Just wanted to say thank you for all that you've done for ALS Research

EdgarAllanPoe9

thank you!

Hello from Greenville! Do you think that ALS will ever be able to be diagnosed early on in life, possibly making it preventable?

norsegod9

This is one of the major areas of the research in the field -- finding biomarkers that would predict the disease before symptoms appear.

Are there any other diseases you think your method will lead to discovering treatments for?

soul_oh

other types of ALS, Alzheimer's, Parkinson's diseases

How big of a role does insufficient Vitamin D levels have on the onset of ALS?

eek-a-hog

Working on it! We do not know yet.

Can you comment on the causes of SOD1 aggregation and misfolding? What types of environmental cues could lead to the clumps other than mutations?

Also, do you think that SOD1 aggregation happens concomitantly with other molecular changes in ALS patients (for instance impaired nucleo cytoplasmic transport, TDP43 aggregation) or rather that SOD1 alone can cause the onset of the disease?

Finally, why do you think SOD1 aggregation affects mainly motor neurons and not (or at least not to the same extent) other cell types in the body?

Thanks for your time

MantisShrimp2

One of the environmental triggers that we found is oxidative stress that promotes dimer dissociation and formation of the toxic SOD1 trimer. There are others.

I'm a medical biotechnologies student; just got a bachelor's degree and still trying to figure out how to work in this field. I'd love to hear your opinion on what requisites, in terms of educational path/career, a foreign student (Italy) should possess in order to find a future abroad.

ashyQL

if you love science, just follow your heart. Understand what is of interest to you, you will find many good schools around the world that would offer great education in the area that you are interested.

Hi Dr. Dokholyan,

One of my good friends has ALS. She was recently put on a feeding tube as the disease has progressed to that point. Her mother died of ALS about 2 years ago, and then right after she passed, my friend was diagnosed with it.

Are you looking for volunteers, or anything like that? We want to keep her around as long as she is willing to stay. She is only 53.

CauseISaidSoThatsWhy

I am so sorry to hear about your friend. Unfortunately I am not a clinician and only work in the laboratory.

Interesting work. How could your hypothesis have been falsifiable?

ChesterChesterfield

Great question. We challenged our hypothesis by designing mutants that would make the trimer more stable. These "super"-mutants killed motoneurons within short time interval. Interestingly, some of the designed mutants turned out to be known FALS mutations. Another test would be to design small molecule (drug) that would interfere with trimer formation and show its effectiveness in organisms.

If my grandfather died from ALS a few years ago, should I be worried about genetic als? Is there gene testing available to look for markers of ALS?

And thank you for what you do in researching ALS.

jeangenie18

Sorry about your grandfather. You can check with 23andme.com. They do genetic screening. I am sure there are other companies.

thank you

Hi Dr. Dokhoylan! Thanks for doing this AMA and congratulations what you've accomplished. Is your paper published online? I'd love to read it - I'm a medical student and so I think it would be very interesting to read!

Thanks!

sourpatchkid3

thank you http://www.pnas.org/content/113/3/614

As a Computer Scientist / Software developer is there any way I can donate some time / computing power to help?

dimensional_dan

absolutely! we are short on manpower for software development. Please contact me via email (dokhlab.org).

So you're saying the 'Ice Bucket Challenge' I took didn't help?

PMMEYOURBUMPYAREOLA

It did raise awareness of the disease and increased donation to ALSA. So I think it was a great success to the field.