Science AMA Series: I am Manolis Dermitzakis, Professor of Genetics at the University of Geneva in Switzerland, I study the genetic basis of complex human traits, AMA!

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

[1]Affiliation not available

April 17, 2023

Abstract

Hello, I am Manolis Dermitzakis (everyone calls me Manolis), Professor of Genetics at the University of Geneva in Switzerland. I will be connecting with you from (surprisingly) sunny Geneva (though it will be dark when I connect) and I am looking forward to reading your questions and try to open a debate about what is important and how we can improve our knowledge of human biology by means of genetic analysis. We have a strong interest in population genomics and genetics of complex traits. We are using various methodologies to understand the role of genetic variation in phenotypic variation. We also aim to understand what fraction of genetic variation is harbored within known functional elements of the human genome, and develop methodologies for their efficient identification. Our main focus is on genome-wide analysis of gene expression and cellular phenotypes and association with nucleotide variation with a focus on disease susceptibility. The questions in our lab range from basic biology of the genome to how we can use molecular phenotypes to understand individual disease risk. However, I am open to all questions outside my comfort zone and I promise I will let you know when I don't know, which may be more frequent than you think I am looking forward to chatting with you! Manolis's current research focuses on the genetic basis of cellular phenotypes and complex traits. He has served as an analysis co-chair in the pilot phase of the ENCODE (ENCyclopedia Of Dna Elements) consortium and member of the analysis group of the Mouse Genome Sequencing Consortium and the International HapMap project. He had a leading analysis role in the extension of the HapMap (aka HapMap3 project) and is a member of the analysis group of the 1000 genomes project and a co-chair in the GTEx (Genotype-tissue expression) project. I will be back at 1 pm ET (10 am PT, 6 pm UTC) to answer your questions, ask me anything!

the WINNOWER

REDDIT

Science AMA Series: I am Manolis Dermitzakis, Professor of Genetics at the University of Geneva in Switzerland, I study the genetic basis of complex human traits, AMA!

MDERMITZAKIS R/SCIENCE

ABSTRACT

Hello, I am Manolis Dermitzakis (everyone calls me Manolis), Professor of Genetics at the University of Geneva in Switzerland. I will be connecting with you from (surprisingly) sunny Geneva (though it will be dark when I connect) and I am looking forward to reading your questions and try to open a debate about what is important and how we can improve our knowledge of human biology by means of genetic analysis. We have a strong interest in population genomics and genetics of complex traits. We are using various methodologies to understand the role of genetic variation in phenotypic variation. We also aim to understand what fraction of genetic variation is harbored within known functional elements of the human genome, and develop methodologies for their efficient identification. Our main focus is on genome-wide analysis of gene expression and cellular phenotypes and association with nucleotide variation with a focus on disease susceptibility. The questions in our lab range from basic biology of the genome to how we can use molecular phenotypes to understand individual disease risk. However, I am open to all questions outside my comfort zone and I promise I will let you know when I don't know, which may be more frequent than you think ☺ I am looking forward to chatting with you!

Manolis's current research focuses on the genetic basis of cellular phenotypes and complex traits. He has served as an analysis co-chair in the pilot phase of the ENCODE (ENCyclopedia Of Dna Elements) consortium and member of the analysis group of the Mouse Genome Sequencing Consortium and the International HapMap project. He had a leading analysis role in the extension of the HapMap (aka HapMap3 project) and is a member of the analysis group of the 1000 genomes project and a co-chair in the GTEx (Genotype-tissue expression) project.

I will be back at 1 pm ET (10 am PT, 6 pm UTC) to answer your questions, ask me anything!

CORRESPONDENCE:

DATE RECEIVED:
November 18, 2015

DOI:
10.15200/winn.144776.62000

ARCHIVED:
November 17, 2015

CITATION:
mdermitzakis , r/Science , Science AMA Series: I am Manolis Dermitzakis, Professor of Genetics at the University of Geneva in Switzerland, I study the genetic basis of complex human traits, AMA!, *The*

Hey manolis! You have worked on nearly every major population genetics discovery sample from hapmap (building a haplotype map of the human genome), 1000 genomes (sequencing of 1000 whole human genomes), ENCODE (mapping functional regions of the genome), and now GTEx (mapping the regulatory network of genes in ~100 different human tissues). Two questions- what do you think have been the greatest successes and failures of these kinds of big data public resources? The genetic material contributed by these subjects must be some of the most studied in the world- how have these resources shaped the landscape of genetics, and how have these resources failed to live up to their promise (given that genetics hasn't been the panacea we all had hoped). And finally, what's next? What large scale population resource would you develop next, if I handed you, say 100 million dollars for the next 5 years?

p1percub

Good question. All these projects gave us unique insight to human biology and we hope to get more by integrating them into a single framework. I am not disappointed and do not think these projects have failed us. On the contrary they provided data and insight that we take for granted that's why we do not

Winnower 2:e144776.62000 , 2015 , DOI: 10.15200/winn.144776.62000

appreciate it. If I had 100M USD I would do a GTEx like project but with more assays (not just genome and RNA) in 30K people around the world to sample diversity both in the genome and environment.

What are your thoughts on companies that promise a detailed analysis of your ancestral ethnicity? Can DNA really tell if someone is Irish vs Chinese vs Brazilian etc?

StarFoxN64

I am always a bit worried about these companies. What ancestry are we interested in? Based on current populations or ancient? Because it is easy to say that one is very similar to inhabitants of Greece today but much harder to say that they are similar to ancient Greeks.

heritability of personality traits is generally observed situationally among individuals; I've even noticed the offspring of one of my pet birds, although raised by surrogate parents in a different house, turned out to have particular, peculiar behaviors in common with the parent.

In doing my psychology undergraduate degree, I would pick twin studies as topics whenever possible, to explore this nature/nurture debate. My findings were disturbing to me personally, as the existing literature and experiments conducted before regulations would have prevented them (twins separated at birth for the purpose of testing this), all (disturbingly) point to nature as superseding nurture.

My question is (ethics of the potential technological implications aside): **Do you think we will ever find genes which are tied to specific personality traits? (or have we already? besides psychopathy/sociopathy I mean)**

Additionally, in the generally-accepted balance of nature/nurture, that is, that genes predispose but external factors affect the expression or degree of expression of said genes, **is science any closer to identifying that factors may be the triggers for the expression of particular genetically-predisposed traits?**

Thank you for reading this

kinetic-passion

I think that there is a genetic effect in everything. The key question is how we define the phenotype. For example, for traits that relate to social behaviour, is social behaviour per se a good phenotype or specific responses to stimuli that in a given context and conditions lead to extreme behaviours? Defining the phenotype well allows for better characterization of the problem.

Kalispera Manoli,

I wanted to ask you a academics-related question which has not much to do with science per se (I hope the users and mods here will forgive me for that).

You are one of the many "top tier" Greek scientists who have decided to follow a career abroad. What do you think are the main reasons that drive scientists away from the Greek universities? (I wanted to ask the same question to Nicholas Katsanis who was featured here yesterday but I totally forgot...)

ravingraven

Science is international. If one wants to do the best science they go where best science is and this is not Greece. I left in 1997, long before the crisis, actually when thnigs were good in Greece generally (not in science necessarily). The fact that things are getting worse does not help. So if your priority is

science leave but if it is your family and friends (which is fine) better to stay.

Hi, thanks so much for taking the time to do this!

I have two questions - one, what is your favorite tidbit, or favorite story, you use at parties and with people who aren't interested in genetics to get them interested in genetics? Or just your favorite "fun fact" to share?

And two, I'm curious what your thoughts are on common ancestors, evolution, or creation, as a geneticist?

Thanks so much!!

Dannyo816

I generally come up with examples that relate to them. Such as family resemblance among themselves etc. Not sure about the question on my thoughts. I have many thoughts depending on the context. But I certainly do not believe in creation, and I think that religion is a great social invention to establish social rules that people follow. As we learn more the space of religion reduces. But as a mentor of mine used to say "If you are to be wrong about religion it is better to believe than not believe"

Can you provide an example of a complex human trait that was reasonably well understood using the modern genomic techniques?

vazdando

Inflammatory bowl disease, blood phenotypes ...

Hi Professor. Have you seen the Norwegian Brainwash series? It tackles the nature vs. nurture debate and interviews both sociologists and biologists/evolutionary psychologists/neuroscientists (like Steven Pinker and Simon Baron-Cohen). The series includes gender, race, and several other topics. Basically at the end of each episode the social scientists are adamant in dismissing inherent biological differences whereas the biologists and psychologists believe both socialization and intrinsic differences are at play.

I know it's controversial but what is your take on it as a geneticist? What role does genetics play on inherent behavioural, physical, and intellectual differences between the genders for example? And as an academic and a scholar, how do you feel when social scientists dismiss evidence supporting biological factors for differences in human populations?

Edit: Added neuroscientist

AyaletSheked

I cannot see how any human action cannot have a "biological" basis. All is biological. Is it genetic? Well. it depends. It is always to some extent but as I said above we need to carefully define the phenotype if we are to ask what is genetic and how much.

Hi Manolis, thanks for doing this AMA! Do you think that everyone should have their genome sequenced (ie requirement for school/healthcare) and see what traits they are likely to have, so that they can receive proper schooling or pursue activities th ey are likely to be good at? Or is it best left up

to the discretion of the person whether they sequence their own genome?

As a follow up, have you sequenced your own genome and found what traits you are likely to have? If so, did your genetic traits match what you observe in yourself?

mynewsonjeffery

I think everyone should have their genome sequenced yesterday! Not only will it slowly provide info about oneself but it will massively improve the understanding of all other genomes. Of course we need to properly record phenotypes etc. I also think e should post our genomes on the internet :-) Yes I know it is extreme but the point is that if we all did that nobody would feel embarrassed or threatened. As I recently said at a debate: "If we were all naked, nobody would feel embarrassed about being naked"

Hi Dr. Manolis and thank you for doing this AMA!

My question is about complex traits. As I am sure you are all too aware, medicine was revolutionized in the 1980's when it became possible to use genetic mapping to locate the genes responsible for Mendelian diseases. Somewhat disappointingly, however, we quickly learned that most diseases do not follow simple inheritance patterns -- they are what we call 'complex traits'. Traditionally, there are at least four way to study complex traits: linkage analysis, allele sharing methods, association studies and polygenic analysis of experimental crosses.

My question is about association studies, which are very much in vogue right now in the biology research community. Simply, I wonder if the community is too reliant on this approach to gain insight into complex diseases. So far, association studies have failed to generate meaningful insight into the genetics of many complex diseases: autism, schizophrenia etc., identifying alleles which account for only a small minority of the total disease. Particularly, troubling to me is the challenge of weaning out false associations in complex populations. For example, artificial association is expected in admixed populations. How do you as a researcher cope with these challenges and do you think that we need to shift more attention to other tools for teasing out the genetics of complex traits?

SirT6

I think that we have learned a lot about the biology behind diseases from GWAS. And we learn more. Yes it was overhyped but at the end it was worth the investment. I truly think that we are at the beginning of a huge revolution in medicine by the implementation of genetic knowledge to complex diseases. But we have not reached the exponential phase yet to see the difference.

What recent findings/discoveries in the field of genetics do you find most fascinating or interesting?

Demon_Slut

CRISPR/Cas9; complexity of genome function (interchromosomal interactions), amount of functional non-coding DNA (not 80% but still a lot)

Is there something, in your field of study, that you think has a real possibility of changing the world and if so how far off is?

Thanks, I appreciate you taking the time to do this AMA!

Scrubera

There are really two ways to bring revolution to medicine. One is to learn deep human biology at the

level of the individual not just the population and the other technology. If you think about it, we know more about mouse biology than we do about humans. We really need to go deep in the biology of each and every human. We are hugely contributing this.

Hi!

I'm currently a first year PhD student in Human Genetics. My goal is to pursue a career in research. Do you have any advice for producing meaningful work and establishing myself in the research community? Also I'm a determined person but it is frustrating when it seems like everything is going wrong with my experiments. Any advice for enduring the frustration and pushing onward to the finish? Any advice in general would be great. Thanks!

howdoihands

Hung in there but make sure you are doing the right experiment and it can work. As a MSc student I sepnt 3 months trying to clone a fragment to a vector, did not work and got a 6/10 grade for this project. Turns out the fragment was deleterious to the vector and the cells and could not be cloned! Talk to your advisor, change project if needed. Also, progress in the PhD is exponential. Most students do 60-70% of the their best work in the last 6-12 months.

Hi Manolis! The work of ENCODE and others was hugely important to human genetics, but it also led to very public debates about definitions (what does "functional" mean?) and less public discourse about whether we gained a deeper understanding of how genetics and evolution work.

Maybe comparative genomics is a better way to understand what ENCODE (and ENCODE-like projects being done in mice and other species) are telling us about human biology. Is more of the genome functional in humans than mice? Does this impact the genetic architecture of complex traits, variation in individual disease risk, and the cadence of natural selection? Are these processes simply driven by population size and generation time, or does studying the functional elements of genomes lead to a more nuanced understanding of these fundamental processes?

arboyko

We have to separate semantics from real biology. Some times oversimplifications bring confusion. Either way we are learning a lot from projects such as ENCODE. Comparative genomics is useful in many ways but it has its limitations. How about human specific enhancers? What do I compare them to to find them? We need to use all resources to learn about the human genome as a whole and individually. But learning about one genome gives us clues about another and I don't think that processes of natural selection, eff pop size etc are changing the genome architecture too much. But doing popgen in the context of genome function is the right thing since regions under some sort of selection are functional (though not all functional regions are under selection)

Why do humans have so many more genetic diseases relative to most other species on this planet?

ToddAC

Many reasons: because we study them more, because we artificially live longer, because we modify our environment and increase the challenges etc.

Hey Manolis, what are you thoughts on the use of CRISPR-Cas9/TALEN on future genetic tests?

Hearthaz

A huge advance. We have to see how it pans out and how we can monitor, regulate its use. Also we need deep understanding of genome interactions before we make changes naively thinking they will only affect DNA interactions locally.

What's your take on those looking to study bioinformatics?

alexslacks

I think more and more biologists should be very comfortable about data analysis and handling of large datasets. So it is basically a requirement not a special talent.

Here's a fun question: how can a layperson get his genome sequenced in an affordable manner?

Here in the US, the FDA has a pretty severe stance on genomic data, leading up to the temporary shuttering of 23andMe due to them using inappropriately strong language suggesting genetic diagnosis.

I went through grad school in a program that had close ties to our institution's genomics program, and I could probably parse my personal genomic data better than your average bear, have fun, and learn a bit more about bioinformatic methods in the process.

I've gone so far as to volunteer for studies that perform exome sequencing and when I requested my genomic data I was informed that the IRB protocol (for redditors who don't know, this is the protocol that protects the use of human subjects in research) expressly forbade sharing of my own biological data.

How do you think we can make the discoveries in genomic more accessible to individuals? How would you propose balancing access with the concerns that people would take genetic correlations far too seriously compared to the certainty of the data?

Cersad

We still need better protocols for citizens to get their genome done. I think it should be their right but at the same time it is our responsibility to get them informed. It is early days but this will happen soon. I don't think we should be the ones telling peole what to do. But we should be educating them so that they make the best choice of how they use their genome info.

Hi Manolis. I am not a biologist, but I remember in my bachelors I had some lectures by a systems biologist. His stance was that breaking biology down into its smallest constituents (genes) had proved ineffective in explaining many aspects of biology, and that the field in general needed to start taking a more "holistic" approach instead of reducing everything to genetics. This idea seems to be directly at odds with your work on the genetic causes of complex traits. How would you respond to this lecturer?

Fenzik

We need both. On the one hand you need the parts but certainly you need the guide of how they interact. Imagine doing medicine with just the body without looking at individual organs or by just looking at the organs without knowing how they communicate in the human body. And no my work is to build up form the parts to the whole. Other build down from the whole to the parts and we hope to meet in the middle :-)

What do you think about the making "designer" babies? Thanks so much for the AMA!

acrim13

NO! NO! NO! Why would you want to do that? The best characteristics of the people I love are their weaknesses which turn into strengths at times.

Hi Professor,

I did my paper on race for one of my high school thesis. I found that the ACTN3 gene, the fast twitch muscle gene that grants faster sprints, was lacking in Asian Americans while it was quite pervasive with the African Americans, particularly in West Africa. Are there more genes that are more likely to be expressed in some races than others?

If this is true, then some might argue there are pretty racist implications in genetics. How do you stop yourself from stereotyping? Is it right or wrong for us to take action according to this research (ex - government policies)?

Thank you for answering my question. I know this is a pretty ethical question, but I would like to know.

the_crowned_jester

There are no races but individuals that sometimes are more related to each than others. If you see it that way then all data will make more sense. Thinking of races is not only ethically wrong but against the data that we have.