Hi! We're Vence Bonham, Eric Green and Lucia Hindorff and we recently published a perspective on how the National Human Genome Research Institute, part of NIH, is prioritizing diversity in human genomics research. Ask us anything!

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

[1]Affiliation not available

April 17, 2023

Abstract

Variations at the genomic level can have huge implications for how we understand our similarities and differences in disease risk, and even for how we respond to certain prescriptions or medical interventions. Part of the goal of The Human Genome Project was the complete mapping and understanding of all the genes in the human genome to begin to uncover these parts of the genome that can vary from person to person. The protocol was to collect blood samples of several volunteers, extract the DNA, sequence it in small chunks, and assemble the pieces back together into one "reference" genome. Except, even before the project launched in 1990, scientists knew that there was no single human genome – and even the small number of individuals whose DNA was used as the first reference genome would not capture all of the variation that exists in the genomes of humans. In 2016, NIH launched the All of Us Research Program to improve the health of all individuals and populations through precision medicine. Precision medicine is a revolutionary approach to healthcare that takes into account individual differences in lifestyle, environment – and especially the differences in our genomes. But last year, a paper published in Nature by Popejoy and Fullerton, suggested that some populations are being left behind on the road to precision medicine. Their findings showed that human genomics research was heavily skewed towards populations of European ancestry and exposed a lack of diverse and underrepresented populations in genomic studies. This disparity must be addressed as the foundation for genomic medicine becomes established. As leaders at NHGRI, one of the 27 institutes and centers at NIH, we are committed to understanding the genomic variation that contributes to health and disease in all populations. We recently published a perspective in Nature Reviews Genetics that lays out the challenges to achieving diversity in genomic research, the ways in which NHGRI has shown its commitment to this significant goal, and the need to engage the scientific community as we move forward. We encourage you to read the paper linked below, and ask us any questions that you have about recruiting diverse participants and communities, scientific impact of diversity in research, funding support for this type of work, and our plan for what needs to be done in both the short- and long-term. Ask us anything! Your hosts today are: Vence Bonham, J.D., Senior Advisor to the NHGRI Director on Genomics and Health Disparities, and Associate Investigator in the Social and Behavioral Research Branch at NHGRI Eric Green, M.D., Ph.D., Director of NHGRI Lucia Hindorff, Ph.D., M.P.H., Program Director in the Division of Genomic Medicine at NHGRI Also joining us today are Larry Brody, Ph.D., Division Director of the Division of Genomics and Society, Teri Manolio, M.D., Ph.D., Division Director of the Division of Genomic Medicine and Maggie Ginoza, B.S., Program Analyst in the Divisions of Genomic Medicine and Genomics and Society. Relevant paper links: Popejoy and Fullerton, 2016. Genomics is failing on diversity. https://www.nature.com/news/genomics-is-failing-on-diversity-1.20759 Hindorff et al., 2017. Prioritizing diversity in human genomics research. https://www.nature.com/articles/nrg.2017.89 UPDATE: We're wrapping up here, but thanks for all of the great questions! We had a blast!

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REDDIT

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NATIONALHUMANGENOME R/SCIENCE

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Eric Green, M.D., Ph.D., Director of NHGRI

Lucia Hindorff, Ph.D., M.P.H., Program Director in the Division of Genomic Medicine at NHGRI

Also joining us today are **Larry Brody, Ph.D.**, Division Director of the Division of Genomics and Society,**Teri Manolio, M.D., Ph.D.**, Division Director of the Division of Genomic Medicine and **Maggie Ginoza, B.S.**, Program Analyst in the Divisions of Genomic Medicine and Genomics and Society.

Relevant paper links: Popejoy and Fullerton, 2016. Genomics is failing on diversity. https://www.nature.com/news/genomics-is-failing-on-diversity-1.20759

Hindorff et al., 2017. Prioritizing diversity in human genomics research.https://www.nature.com/articles/nrg.2017.89

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WRITE A REVIEW

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Hi Vince, Eric and Lucia, and thank you for doing this AMA!

From the perspective of precision medicine, I completely agree that we need to do a better job of capturing natural population diversity in our genetics research.

From a basic biology perspective, how do you interpret results where an association in people of European ancestry fails to replicate in individuals of a different ancestry? For example, the first paper you link writes:

For example, for 25% of the variants in European Americans that GWAS have identified as being associated with body mass index, type 2 diabetes and lipid levels, the strength of the association differs in at least one out of five populations of non-European ancestry. This means that a variant that is associated with diabetes may confer a different risk of disease in someone of European ancestry than in, say, an individual of African ancestry.

What do you reckon is happening in these cases? Is the biology fundamentally different (i.e. compensating alleles)? Is the math broken (i.e. poorly powered post-hoc analyses)? Is it some cultural/environmental factor modulating the genetic influence of the allele of interest?

SirT6

Hi, this is Larry Brody. We do not have evidence that the biology is different. The math is usually correct for the studies as reported. The problem arises when extrapolating these findings. As scientists, we should be more careful about describing the participants in our studies. When we say "25% of the variants in European Americans," what we really mean is that the findings we are reporting were found in European Americans who happen to participate in the study. In addition to their ancestry, all study participants bring along all their social and environmental "exposures." We need to do a better job of capturing these as well. You can easily imagine finding a connection between a genetic variant in European Americans who live in Arizona and not see that same association in folks with the same ancestry who live in Seattle (think vitamin D levels, skin cancer, and other phenotypes (or outward expression of genetics) related to sun exposure). In other words, you are correct. The most likely explanation is that yes, as you state "some cultural/environmental factor [modulates] the genetic influence of the allele of interest."

This is on Reddit! I attended a seminar by Vence Bonham not long ago at work and was impressed by all the passionate people there to improve health care equity and precision medicine. With the goal of equal representation of varying people from varying backgrounds, I have a statistics question. Can the sampling for the All of Us study take into account population bias up front? If you want a large organized collection of data to best represent the entire American (or beyond) population, doesn't it make sense to predetermine a sort of subgroup-population-limit for each possible demographic? Since this study is also taking environment into account my example would be: 10k high socioeconomic status African Americans, 10k low socioeconomic status African Americans, 10k high SES Caucasians, 10k Low SES Caucasians, 10k high SES Pacific Islander, 10k low SES Pacific Islander... etc. etc. you get the point). This way all populations will be equally represented by the data and it is helpful for anyone accessing it. Now, I know there is granularity that is likely to be missed. I am sure some less accessible demographics, like Innuits who are vegetarians, might be difficult to represent but I think we could highlight a good number of different groups of people that most obviously need represented. Although, If we can do it, the smaller and more unique these subgroups the better!

dat_throw_aw4y

Hi, this is Teri Manolio. One of the goals of the All of Us study is to recruit as diverse a population, as possible (that is, including as many subgroups of the US population), but there is not a pre-specified goal of equal representation of varying subgroups from varying backgrounds. Another goal of All of Us is to include everyone who would like to join, so there will be no limits to any demographic subgroups. A third goal is to characterize the participants as well as possible, which will permit identification and analysis of unique subgroups for analysis. Choices of subgroups for analysis will be driven by the scientific questions being asked, and may well produce an analysis such as you describe, with multiple equal-sized subgroups, to the degree that they are included in the final All of Us cohort. More information about the All of Us Research Program can be found here: https://allofus.nih.gov/

Hi, epi nerd here, couple questions:

Since finding genetic links to disease completely mandates knowledge of environmental/lifestyle factors in order to control for them, why are we only speaking about the lack of diversity in terms of genomic diversity, when it's equally as important to have diversity of environment to do this kind of science? Your response paper talked about higher cancer survival rates in white women (no shocking news there) but also noted that

"As only limited environmental factors were available in TCGA, the environmental contribution to understanding cancer health disparities could not be assessed..."

You list a number of factors which distinguish under-represented groups from the majority population in historic genome research, such as

"socioeconomic factors (such as lack of discretionary time, loss of income owing to time away from work or lack of access to transportation and information resources), cultural factors (such as language differences) or health research-specific factors (such as poorer overall health status and greater mistrust of research or health care systems)... limited access to basic health care"

To a social epidemiologist, these are not just marginal characteristics which impede research, but factors which make the people different and important to include in your study. That is, isn't this kind of diversity *just as important* as genomic diversity in looking for predictors of disease?

I guess my main question is, why are we talking about diversity solely in terms of genomic diversity (wherein we erase every other aspect of a person aside from their genomic data) instead of valuing diversity as a holistic concept of being human (including environmental/lifestyle factors), especially given what we know about environmental predictors of health outcomes?

sublimesam

This is Lucia, fellow epi nerd! Thanks for the really great questions! One thing I want to emphasize is that we do not equate race/ethnicity with genomics, or consider genomics the only (or even main) source of diversity. Diversity captures both genes and environment and we need to understand both aspects to understand human health and disease. An early effort to understand the joint contributions of genes and environment was the Gene Environment Association GENEVA study (https://www.genome.gov/27541319/gene-environment-association-studes-geneva/), a consortium of investigators funded to examine how genotype-phenotype associations vary by environment. We've been building on that work ever since. One of our strongest recommendations in the Perspective (https://www.nature.com/news/genomics-is-failing-on-diversity-1.20759) is to consider both genomic and environmental contributors at the levels of designing a study and formulating a research question (see Table 3). Because NHGRI's core mission focuses on genomics, many of the NHGRI-related projects will have a primary focus on genomics, but we are also interested in how genes interact with environment.

Thanks for doing this event! What are some of the biggest practical and ethical hurdles in recruiting diverse participants for genome research?

kiri-kin-tha

Hi, this is Vence! Great question! It is important that when recruiting participants in genomic studies that you inform the prospective participant about the objectives of the study and be clear that they will not necessarily benefit from participating in the study as an individual. In the past, there have been ethical abuses in research that have created mistrust among some regarding participating in research in research studies (e.g. U.S. Public Health Services Syphilis Study (https://www.cdc.gov/tuskegee/timeline.htm); and the Guatemala Study http://www.nytimes.com/2010/10/02/health/research/02infect.html). As researchers, we must learn from those experiences to create an ethical environment for research.
It is important to know that a number of studies have documented that individuals from diverse communities are willing and interested in participating research (http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0030019) and that we have an obligation to invite individuals from diverse backgrounds to participate in genome research.
An additional practical consideration is that we need to increase the number of scientists who come from diverse backgrounds.

How do you ethically respond to situations where an individual's self reported ancestry may be in conflict with their ancestral formative markers?

rdflme

Lucia and Larry, tag-teaming this one! When individuals receive conflicting or confusing information about ancestry, it is often because their genetic information may suggest their ancestors came from a different region of the world than they expected. The best ethical response deals with this issue in advance. Anyone who is taking a genetic test should be informed about the possible outcomes. This process of informed consent will allow a person to decide not to get tested in the first place. Unfortunately, this process needs streamlining beyond the long, complicated agreements that we see and "click through" (and never read) when we download a new app, for example.

There are a number of reasons as to why someone's self-reported ancestry does not match what a genetic test may reveal. For many of us, our relatives may have come from more than one geographic region so our genetic ancestry is considered mixed rather than belonging exclusively to one group or another. We are learning more and more about how predefined race categories may be useful for administrative purposes, but do not capture the complexity that defines how an individual reports his or her ancestry.

One cool scientific observation that is starting to be recognized is that ancestry is more of a continuum that we thought. For example, for the genetic epidemiology nerds, like myself (Lucia) - take a look at Figure 1 of this preprint from the PAGE program: (https://www.biorxiv.org/content/early/2017/09/15/188094). You can see on the left side how many individuals fall on a spectrum of the broad race/ethnicity categories. (You see a group of individuals colored with yellow dots (Asian) falling along more of a line than a clump.) However, if you take one of those broad groups, Hispanic/Latinos, and do a more fine-grained analysis, you see a similar spreading of dots across a line rather than a clump (right side of Fig. 1). So even the race categories themselves are a lot more complex, and what we think of as an individual race may be more of a spectrum.

Forgive me if this is a stupid question.

When people talk about DNA not repairing properly with age, does that mean the entirety of your DNA, or could you have a problem in one place on your body but not a problem in another place?

ScotchmanWhoDrinketh

Larry, here! No such thing as a stupid question, but you are correct! The efficiency of DNA repair does differ in different parts of your body. More importantly, the exposure of your cells and tissues to bad things, e.g., chemicals, light, gases, differs greatly. Think about cigarette smoke. This toxin directly hits your mouth, throat and lungs. We need DNA repair to work well to prevent cancer. It is no coincidence smoke associated cancers arise in tissues that are flooded with the DNA damaging components in smoke. Another factor is how often the cells are dividing. The errors in DNA repair that lead to cancer are most frequently found in cells that keep dividing.

Could (assuming there is any) pressure to recruit study participants from diverse backgrounds have unintended consequences that result in abuse or exploitation?

craftsroom

Vence, here! As we discussed in the article "Prioritizing diversity in human genomic research" (https://www.nature.com/articles/nrg.2017.89) recruitment of individuals from diverse backgrounds is a scientific imperative for genomic research. No individual should be recruited to participate in a study without being fully informed of the benefits and risks or pressured to participate in a study. I addressed this further in my response to user kiri-kin-tha in a different response on this AMA, so check that out as well. As researchers, we have a responsibility to follow the ethical principles and guidelines for conducting research involving human subjects. (https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html).

How much does this impinge on ethical practice considerations?

ThatAtheistPlace

Hi! Maggie, here! From what we have seen, prioritizing diversity falls right in line with ethical research practice! By ensuring the inclusion of diverse participants, we can then extend the benefits of genomic research to all groups, without excluding any particular population.

Why do you have Hispanic/Latin American ancestry as a separate group and why are they listed as non-European? Beyond lifestyle and environment data, it's not a real group. The samples would fall under European, Native and mixed ancestry. If you are trying to attract more Latin Americans you probably shouldn't describe them as non-European.

bitchalot

Lucia, again: One of the standard ways of measuring inclusion in NIH-funded studies is for investigators to report the numbers of study participants that fall into different census categories of race and ethnicity. For this standard, it was decided that race and ethnicity would be reported separately. Ethnicity was defined as Hispanic/Latino or not Hispanic/Latino. White (which includes Europeans) is a separate race category. All these categories are geographically and socially derived and have limitations.

I've noticed a number of health care providers using terms like precision medicine, or personalized medicine, or treatments tailor-made for you. (As well as drug commercials that seem to target a very very specific subset of patients). Does the general public have an adequate understanding of this concept? Is there a certain amount of "hype" that we need to watch out for?

craftsroom

Many use these terms interchangeably, whereas others consider them to have slightly different meanings. So to be honest, it is difficult to imagine the general public would always have a good understanding of what is meant by each. We're probably safest in defining precision or personalized medicine as treatments selected for an individual patient based on what we know of his/her unique genetic and behavioral characteristics, environmental exposures, and personal preferences. It will also be difficult to truly achieve "treatments tailor-made" for each individual; so, yes, it will be important to avoid hype in discussing these advances. -- Teri Manolio

Hi, and thank you for this AMA!

I'm currently involved in genomics research, but at a lower level-I'm a research coordinator. However, I plan to stay in this field, and hopefully move up. It's exciting to see more focus on this topic, in yours and recent articles. However, working in a predominantly wealthy and caucasian health system, I do not see engaging minority and lower-income populations in genetic research, within my own health system and others, being given much attention and especially, action, by those with policy influence.

So my question is, since this is an area of passion for me, what can the next generation of scientists, like myself, do at this time to help this area get more attention and focus?

Thank you!

823freckles

Hi, this is Eric Green. For starters, let me applaud you for your passion about this important topic and its associated complex issues. Having highly engaged professionals, like you, with an appreciation of the importance of ensuring diversity in genomics and genomic medicine implementation will be critical for ensuring health equity. There are a number of ongoing research efforts, many of which are mentioned in our Nature Reviews Genetics article (https://www.nature.com/articles/nrg.2017.89?WT.feed_name=subjects_scientific-community-and-society), that aim to enhance diversity in 'all-things genomics'; in the long-run, such efforts will need champions to conduct the research and to disseminate best practices across different settings. I would urge you to stay engaged, spread the word, and bring your passion to these ongoing and future efforts. I honestly believe there will be meaningful opportunities for professionals of various types to help in getting more attention and focus to this important area. Hopefully, you will be among them!

Hi, I'm a data analyst and acrobat. How will you ensure a sufficient sample of data from circus performers in your genomic studies, and how will this influence your findings?

cirquedusammy

Hi, this is Maggie! Funny enough, when I'm not busy working at NHGRI, circus is one of my hobbies! To our knowledge, there has not been any genomic research conducted focusing specifically on circus performers. If someone wanted to do such a study, they would need to plan engagement and recruitment strategies that are able to reach the diverse communities of circus performers around the world. Circus covers a broad range of disciplines, and includes people from many backgrounds, so this could be a big feat! I can see overlap here with current popular interest in the contributions of our

genes to traits such as elite athletic ability. Perhaps we could learn something interesting about similar characteristics in circus performers such as strength, coordination, or flexibility.

Thank you for doing this AMA!

Excuse my shallow question but: How much time does it take to make a diverse population for the study?

bronxyle

How much time do you have :)? There are many ways that recruiting a diverse research population can be more complicated than expected. Previous studies cited in our paper describe some of the challenges of recruiting diverse and underserved populations (see these papers: https://www.ncbi.nlm.nih.gov/pubmed/16533107, https://www.ncbi.nlm.nih.gov/pubmed/24328648) -- for example, someone may have trouble taking time off of work to participate in a research study. Someone else may have trouble with the language. The amount of time and effort it takes depends on the type(s) of participants being recruited for the study and on the study's scientific goals. Furthermore, different populations may present unique challenges for recruitment. Many of NHGRI's research projects require several years (three or more) for recruiting a suitable study population.

What do you guys believe is the biggest challenge to the commercialization of genomics?

Ohsorich05

Larry, here! Genomics refers to a wide range of technologies and applications. Many of these have already been commercialized. In our research labs we use a number of commercial instruments to study genomics. These were not available even a few years ago. Genomic technologies are widely used in agriculture to measure the genetic makeup of plants and animals so that good traits are preserved and bad traits are bred out. (Note, this is not the same process as genetically engineering plants and animals.)

Genomic technologies are becoming increasingly important in medicine. There are a large number of companies who offer diagnostic tests to the medical community.

You can read more about the economic impact of the Human Genome Project (https://www.genome.gov/11511417/what-is-the-human-genome-project/) here and in the report to which this page refers:

https://www.genome.gov/27544383/calculating-the-economic-impact-of-the-human-genome-project/

Hello, thank you for your time

Does there appear to a ranking among regional DNA, across the World, as to hardiest or some other desirable trait?

Also, what are your thoughts on Net Neutrality?

lurking_digger

Interesting question. This is Larry...I'll take a stab. The DNA of each person (even identical twins) is unique. There are DNA variants (or sections of the genome that vary from person to person) that we can use to reconstruct the history of human populations. These sections are chosen because they are found at different frequencies in different regions. In almost all cases, these variants are simply

markers and do not change how the gene functions.

There are a few genes in which variants have been describe to have an advantage in certain environmental conditions. The two best known are 1) variants found more frequently in Africa and Europe that allow adults to digest milk. 2) Variants that increase the ability of people to live at very high altitude (in South America and the Himalayas).

The above situations arose a very long time ago as people moved to different environments. Such examples are rare and they are probably not relevant today as humans have become very good at changing their environment.

As such, questions about hardiness and desirability, like beauty, are more in the eye of the beholder.