

Science AMA Series: Why are some people more likely to develop diabetes than others? We are researchers putting genes and lifestyle together. Ask Us Anything!

T2DGenes¹ and r/Science AMAs¹

¹Affiliation not available

April 17, 2023

Abstract

Hi Reddit! We are leaders of a global research effort to identify and characterize the mechanisms responsible for the development of type 2 diabetes (and related conditions including obesity) using human genetics. The prevalence of these conditions continues to increase, and current strategies for prevention and treatment are clearly inadequate. We perform large-scale discovery studies (using genotyping and next-generation sequencing in tens of thousands of individuals) to highlight the variants that influence individual predisposition to these conditions. We then use these discoveries as the starting point to home in on the specific mechanisms through which those genes act, providing novel clues to disease biology. We hope to turn this information into new ways of treating and preventing these conditions. Our latest study (including GWAS, exome array, exome and genome sequencing in 120,000 subjects) was just published in Nature (you can read here). This study provides the most detailed description to date of the contribution of inherited genetic variation to T2D risk: it has established that shared common variation underlies most of that predisposition, as well as identifying a number of genes which are disrupted as a result of those changes, and which are therefore prime targets for future therapeutic development. You can find out a bit more about these studies in the blogs here. An important facet of our efforts is being proactive about sharing those data with other researchers (for example). We are: Mark McCarthy, University of Oxford, UK Mike Boehnke, University of Michigan, US Andrew Morris, University of Liverpool, UK Jason Flannick, Broad Institute, US Christian Fuchsberger, University of Michigan, US & EURAC, Italy Tanya Teslovich, University of Michigan. We will be back at 3pm EDT (noon PT, 8pm BST) to answer your question, ask me/us anything! Thanks everyone - we're signing off now. Been fun. Sorry we didnt get to every question but hope you have found it useful. Best Mark (on behalf of the team)

[REDDIT](#)

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T2DGENES [R/SCIENCE](#)

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We are:

Mark McCarthy, University of Oxford, UK

Mike Boehnke, University of Michigan, US

Andrew Morris, University of Liverpool, UK

Jason Flannick, Broad Institute, US

Christian Fuchsberger, University of Michigan, US & EURAC, Italy

Tanya Teslovich, University of Michigan.

We will be back at 3pm EDT (noon PT, 8pm BST) to answer your question, ask me/us anything!

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CORRESPONDENCE:

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My coworker eats a sugar free, low carb diet and does exercise at least 4 times a week for 30 minutes. She has just found she has high blood sugar levels. Her Dad's side of the family all have type 2 diabetes. How is she meant to fix this? We joke about her having to eat cardboard.

[notherme](#)

Mike: Type 2 diabetes is a complex disease, with genetic and behavioral factors both important in determining disease risk. Given a high family risk (which could be genetic or behavioral or both), I personally would try to be extra careful about eating a good diet and getting plenty of exercise. I would not opt for cardboard. :)

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Well, here we go: Why *are* some people more likely to develop diabetes than others?

I know this sounds like a joke but I mean it. I always thought it was small part genetics, large part diet. Are you investigating these parts in more detail or are you investigating other factors (environmental, lifestyle, whathaveyou)?

[DeVadder](#)

Hi Mark here, just kicking this off a little early. Thanks to everyone for the many questions. Though I am a physician (my co-researchers are not..), we are mostly going to focus on the more research questions (such as this) rather than trying to answer specific clinical questions. Well, that's the plan - lets see what happens. Havent done one of these before, so interested to see where we end up...

the way i think of this is that there are a whole raft of different factors that can push up or down your risk of developing (type 2) diabetes. (Assume that when we say diabetes we mean T2D in the context of this discussion, unless we say otherwise!). Some of those are genetic (more on that in a moment), some are related to environment. By environment, I mean pretty much everything that impinges on you during your lifetime from the cradle (and before) to the grave. We know for example that diabetes risk is influenced by events in utero (whether you had a good food supply in the womb; or whether or not your mother had diabetes during the pregnancy). Then of course diet, exercise, other factors (shiftwork etc) during adult life, plus other factors we dont understand. There's the impact of ethnicity (which may be a combination of genetics, environment, and early life factors). Returning to the genetics, for most people that's not just one genetic change, its a combination of many different variants that you inherit from your mother and father some of which increase your risk, some decrease.

In any one person, one or other factor may be a bit more important than others, but for most people with "typical" disease its a combination of many smaller factors...

Mark

Well, here we go: Why *are* some people more likely to develop diabetes than others?

I know this sounds like a joke but I mean it. I always thought it was small part genetics, large part diet. Are you investigating these parts in more detail or are you investigating other factors (environmental, lifestyle, whathaveyou)?

[DeVadder](#)

Mike: There are definitely both behavioral and genetic factors involved. Part of the reason for focusing on genetic factors is they are easy to measure (compared to say diet and exercise) and you only need to measure genetics once.

can you comment on the role the gut microbiome plays in the development or protection of diabetes?

i understand we can induce Type 2 in transgenic mice by giving them antibiotics. I would also be curious if restoring this microbiome could help reverse the pathogenesis of the disease.

Thank you very much for this AMA

[angry_doc](#)

microbiome

Mark here - good q. Very hot topic. No doubt that folks with diabetes have different microbiome to those without, but still unclear what is cause, and what is effect. One recent paper in Nature showed that a lot of the apparent differences between type 2 diabetes and not diabetes microbiome result from the effects of metformin, and that if you account for that the differences are less extreme. It has been suggested that one of the ways metformin works is by "normalising" the microbiome.

Certainly evidence from rodents that fecal transplants can "cure" obesity, and these are now routinely used in humans to treat intractable gut infections (with *Clostridium difficile*). Some initial (small scale) evidence that they have an impact on obesity and diabetes too but much larger studies needed.

Genetics can help here. Some studies likely to emerge in the coming year showing which DNA sequence variants have an impact on the microbiome that you have. If it turns out that some of the variants are the same ones that have been implicated in differences in risk of obesity or diabetes, it will be a pretty major step forward in demonstrating that the microbiome is a causal factor in diabetes/obesity (and not just a reflection thereof). We should know a lot more in a year or two on this.

Mark

This is a two parter -

1 - Some neurodegenerative diseases have been described as 'diabetes of the brain', which suggests that underlying defects of energy metabolism/uptake may be common across multiple tissues/diseases. In identifying genetic etiologies, have you found any surprises involving mutations affecting tissues other than the pancreas?

2 - Are there any non-presenting heterozygote mutations that have been identified as having a protective capacity, akin to heterozygotes for SCA having increased immunity to malaria?

Just kidding 3 parter - Are there any populations that were surprisingly at risk, or any populations that were surprisingly low risk?

Thanks!

[lzawwlgood](#)

Jason here. With respect to Q #1, the main tissues we traditionally see T2D-relevant genes acting through are the pancreas or insulin responsive tissues like muscle, fat, and the liver. MC4R is a gene that was implicated in T2D risk, as well as in effects on BMI (it's still debated whether the genetic risk factor is entirely due to weight gain, which causes T2D, or whether there are effects on T2D independent of T2D), and it is mostly expressed in the brain (<http://www.gtexportal.org/home/gene/MC4R>). Another cool gene is FTO, which like MC4R is associated with BMI in addition to T2D. This was at one point proposed to act through the brain (<http://www.nature.com/nature/journal/vaop/ncurrent/abs/nature13138.html>) but more recently was proposed to act through brown fat, or a type of fat that's responsible for generating heat (<http://www.nejm.org/doi/full/10.1056/NEJMoa1502214>) and has received a lot of attention as an attractive therapeutic mechanism

Re: Q#2. In fact the data used in our study was also instrumental in identifying mutations in a gene (SLC30A8) that seem to cause reduced activity and protect against T2D (<http://www.ncbi.nlm.nih.gov/pubmed/24584071>). These aren't fully like SCA, in that homozygotes (which we haven't identified) wouldn't be expected to have any detrimental effects, but this gene could potentially be an attractive therapeutic target (although much more work is needed).

Q#3: our study looked more at population specific genetic effects, rather than overall risk across populations. A cool example of how high risk populations can harbor novel genetic effects are variants

found in the Mexican population (<http://www.ncbi.nlm.nih.gov/pubmed/24390345>) or the Inuit population (<http://www.nature.com/nature/journal/v512/n7513/full/nature13425.html>)

I am a health economist, and while the genetic aspects of the disease are beyond me, I am curious, in your opinion, as to what role you think economics (be it incentives or behavioural economics (behavioural psychology)) interventions could (a) lead to a decrease in the risk or incidence of diabetes (b) improve health outcomes (clinical, quality of life, and indeed health resource (GP visits, hospitalizations, etc) for diabetes patients.

[ar_604](#)

Hi there, Mark here, thx for the question. Not my field, but a huge amount of work underway in this area, trying to work out what behavioral interventions might be of benefit. Noone's cracked that quite yet in terms of finding a magic bullet. Lots of debate as to whether the solution is public health measures (e.g. sugar tax...) or personal tailored intervention.

Part of what genetics can do is help us sift thruhg the many environmental exposures and help work out which ones might be most important. Its tempting to say that its "western lifestyle" but obviously that consists of a whole pile of correlated exposures. Would be great if we could work out which ones are most critical, and genetic can help here by pointing to the right mechanisms

Mark

Does your research indicate any dietary changes that would actually prevent the development of T2DM in people with a strong genetic predisposition? I come from 4 generations of women who died of complications of diabetes (mostly strokes and heart attacks). I've adopted a ketogenic diet on the premise that if I don't spend a lot of time causing spikes in Blood sugar, I wont develop the resistance. The traditional diabetic diet is actually quite full of carbohydrates.

[agawl81](#)

Hi - Mark here.

As you'll know there's a huge amount of controversy on this. One view is that from the perspective of obesity, its about energy balance (calories in, calories out; simple laws of thermodynamics) in which case its really just total calories that matter. There's others who emphasise more what the balance of calories is. Is dietary fat particularly bad for you (calories being equal), or refined sugar? Perhaps through changes in gut microflora. Still far from clear.

So in direct answer to your q, i really think its about what we consider these days a sensible diet. Balanced in terms of major food constituents, fresh as much as possible (not processed).... there is no absolutely definitive evidence yet that there's particular merit in avoiding any specific component (though I would personally keep the sat fats down, the refined sugars, processed foods etc).

Does your research indicate any dietary changes that would actually prevent the development of T2DM in people with a strong genetic predisposition? I come from 4 generations of women who died of complications of diabetes (mostly strokes and heart attacks). I've adopted a ketogenic diet on the premise that if I don't spend a lot of time causing spikes in Blood sugar, I wont develop the resistance. The traditional diabetic diet is actually quite full of carbohydrates.

[agawl81](#)

Jason here. This is outside of our research area, so I'm not in a position to comment on anything related to personal care. But, this research paper on predicting nutrition based on glycemic responses (<http://www.ncbi.nlm.nih.gov/pubmed/26590418>) did come to my mind if you are interested in reading up on some relevant research (again, should be viewed only as research and in no way any sort of recommendation)

What is your input on recent studies (mentioned Dr. Neil Bernard, Dr John McDougall, Mr Michael Gregor) that suggest it's not the sugar that initially *brings on* diabetes, but is instead too much fat intake that effects the pancreas? They claim they see type II diabetes being reversed on low fat, plant based diets.

[hardyhaha_09](#)

Mark here: yes, this is really interesting data. The idea that pancreatic fat might be a key player. Certainly looks as if very low calorie diets (which reduce pancreatic fat, along w fat elsewhere) have a strongly beneficial effect on diabetes. Not yet conclusive that the reduction in pancreatic fat CAUSES the improvement in diabetes, but its definitely a strong hypothesis that many are following up. The UK Biobank ahs started to do MRI analyses on 100,000 participants (about 10K done as a pilot) so this will be a rich source of data that might be able to tease apart the precise role of pancreatic fat. M

Can a change in lifestyle cure type 2 diabetes?

[PokemonGOFuckUrself](#)

Lifestyle interventions are probably the most effective way we have to delay onset of T2D (see a seminal study here <http://www.nejm.org/doi/full/10.1056/NEJMoa012512>). I don't know whether I would qualify this as a "cure"

Is it possible that some of the genetic factors that correlate with diabetes do not actually cause diabetes themselves, but rather predispose people to bad lifestyles?

[augustoph](#)

Mark here.

Possibly. Prefer not to talk about "good" and "bad" lifestyles, but I know what you mean. There's been a bit of work around the variants implicated in obesity risk as to whetehr they impact on food preferences for example, or exercise potential. Nothing too conclusive (and htese are hard things to measure in free-roaming humans). But for sure, some of these genetic factors may well work through some impact on the frequency of an adverse exposure (eg promoting dietary intake), or on the consequences of that exposure. We've looked for taht, but not seen anyting conclusive so I suspect this isnt a major explanation of what's going on.

Thanks for coming today! It's often hard to know the impact of a variant that isn't located anywhere near a gene or known binding site. In your work, how do you address the challenges of interpreting the biological meaning of whole genome sequence data?

[p1percub](#)

Jason here. Very good question. Interpreting the impacts of noncoding variants is one of THE most

important question in complex trait genetics today. Since most noncoding disease-related variants are thought to affect regulation of gene activity (rather than breaking a gene directly), methods in existence today focus on predicting regulatory effects of variants. This is done through (a) testing to see whether the variant, in addition to being associated with disease risk, is also associated with expression levels of a gene (called eQTL mapping; see <http://www.nature.com/nrg/journal/v16/n7/full/nrg3969.html>) or (b) seeing whether a variant is predicted to affect a regulatory element in the genome (much of the "dark matter" in the 99% of the genome that doesn't code for proteins; see <http://www.roadmappigenomics.org/>). In our work we focused mostly on (b), seeing whether variants overlapped with predicted regulatory annotations. We weren't able to show any "smoking gun" noncoding variants that clearly affected gene expression, but we were able to show that affecting regulation of genes in pancreatic islets does seem to be a pathway through which many genetic variants act.

Thanks for coming today! It's often hard to know the impact of a variant that isn't located anywhere near a gene or known binding site. In your work, how do you address the challenges of interpreting the biological meaning of whole genome sequence data?

[p1percub](#)

Mike: Really good question, and one that we and many in the field are working to address. It is not easy. Beyond genes and binding sites, we seek to identify other ways to characterize regions of the genome in terms of function or physical characteristics that make them potentially of interest. We can then ask the question: are the disease-associated variants we are discovering enriched in the corresponding regions? Lots to do.

My dad had type 2 diabetes (he got it about 30 years before I was born). Does this increase the chance of me developing type 2 diabetes? (we have no other known history of either type 1 or 2 diabetes in our family)

[smitingblobs](#)

Andrew: a family history of type 2 diabetes is associated with increased risk of the disease. However, there are many genetic and environmental risk factors, so the fact that your dad had the disease does not mean you will get it for certain.

I actually have a different kind of question than the rest that I see here. Namely, I am really intrigued about how all of you have become interested in studying the biological mechanisms underlying type 2 diabetes in particular? Was it a coincidence that you had the opportunity to get involved in research on this topic or rather something that you wanted to do for a long time?

[sagefaciens](#)

Mark here. Thx for the question. I was training as a physician (in endocrinology) and stepped out for a few years to do some research (as many medics do). The dept i was in, was working on the genetics of type 2 diabetes and i started (naturally, by default) working on that. But having fallen into the area by circumstance, its now become the focus of my research life. And I pleased about that. I still see patients a couple of times a month and that motivates me in my research. I can see what the disease does to people, (and I know from the figures how much of an impact it makes to society etc), and i am hopeful that our research is, piece by piece, building up the store of knowledge that will allow us to do a better job of treating and preventing this disease that affects around 1 in 10 humans on the planet.
Mark

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[sagefaciens](#)

Mike: Back in the early 90s, a colleague and I decided to pick our next disease to study. We chose a set of criteria and then went away to think. A week later when we got back together, I said "NIDDM" and he said "NIDDM". NIDDM is non-insulin dependent diabetes, which we now call T2D. One of our criteria, misguided as it turned out, was "a disease with not too much competition". The key to our success in T2D genetics research, along with advances in technology, has been to turn competition to collaboration, so having lots of "competitors" turned out to be incredibly valuable.

Hi everyone, and thank you for taking the time to do this AMA. A couple of questions for you:

- How many individuals (of the 100,000+ you sequenced) were carriers for one of the alleles that you find to be associated with T2D (and how does this compare to what you would expect based on allele frequency in the population)? How many were carriers of more than one allele? Did you make any observations about carrier status and disease pathology (age of onset, severity, resistance to treatment etc)?
- Looking at Table 1 in your paper, it is striking that many of the alleles that you find as linked to T2D are so common. Did this surprise you? Looking at the odds ratios for these alleles, it seems that the impact they have on whether an individual is likely to have T2D is relatively minor (with the exception of PAX4). How do you interpret this observation?
- You note that many of these risk alleles are non-synonymous. Did you make any attempt to predict whether they would impact protein function (e.g. do the SNPs occur in important domains of these proteins)?
- You conclude your Discussion by suggesting that rare variants are unlikely to contribute to T2D. Does this consider the possibility of combinations of one or more rare variants may be important?

[SirT6](#)

Jason here. In answer to your first two questions, the main finding of this study is that most people's genetic predisposition to T2D is determined by combinations of many (hundreds or maybe even thousands) variants, almost all of which will be common in the population (over 5% of people carrying them). So everybody carries at least one, and likely many, variants that are technically associated with T2D. The fact that these variants all individually have very small effects on T2D risk (5-10%, so carrying one would increase your chances from 8% to 8.1%) was one of the first findings to come out of genome wide association studies back around 2010, so it's not surprising that the odds ratios are small. However, what was debated

(<http://www.nature.com/nature/journal/v461/n7265/full/nature08494.html>) was whether risk for T2D (and other complex diseases) was *mostly* due to these variants or only partly, in which case most of the risk would be due to high effect variants. Our study seems to suggest that in fact common variants of weak effect contribute to the vast majority of the genetic basis of T2D.

We did make some effort to predict which alleles impact protein function; Figure 1 (if I recall) shows that predicted damaging variants, at least those in specific sets of genes, have stronger effects than those predicted as having no effect

Rare variants definitely may be important, and almost certainly there are rare variants of high effect on T2D (see Figure 1, also <http://www.ncbi.nlm.nih.gov/pubmed/24584071>, <http://www.ncbi.nlm.nih.gov/pubmed/25157153>). But, in terms of what determines genetic T2D risk in the *population*, common variants seem to be the most important.

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[SirT6](#)

Andrew: as Jason says, many of the variants identified for type 2 diabetes are common in frequency (and typically common across diverse populations). This is true for most common human diseases. This doesn't mean that rarer variants aren't causal for type 2 diabetes - but rather that we haven't had big enough sample sizes (even 100's of thousands) to see these effects yet.

I heard on the radio a few years ago about a study of about 50 subjects in which a significant number managed to reverse their diabetes by eating a very low calorie diet for x months. Their body supposedly starts making insulin normally again.

Have you heard of this study? What are your thoughts on this?

Thank you for your time :-)

[GoodOIBluesBrother](#)

Mark here - yes you remembered correctly. Very interesting data. Looks real. It's a very low calorie diet (not everyone can manage it).

As you may know, bariatric surgery (for obesity) also has a dramatic effect on diabetes in some people, with resolution of the diabetes even before much weight loss has occurred.

Unclear what the mechanisms are here. Some have suggested that rapid reduction in the fat in the pancreas is responsible. Others that there are dramatic changes in the gut microbiome that result. Others that it's due to the changes in gut hormones that result.

Lots of research going on to disentangle these. The effects are dramatic, and the hope is that if we know HOW these interventions work, that we might be able to reproduce the impact with something a

little less dramatic and a little more acceptable to everyone.

Lets hope. Exciting times.

My father was a healthy weight when he was diagnosed with T2D in his early 40s. My paternal half-sister is overweight and was diagnosed in her 30s. My paternal half-brother is tall, fit, and athletic but was diagnosed as pre-diabetic in his late 30s.

I am 28f, 5'9, 143lbs and I walk a lot. I used to have frequent episodes of non-diabetic hypoglycemia, sometimes even immediately after eating a meal (this frequently happened to my father as well, but he had gastroparesis); they are mostly under control thanks to dietary changes.

Am I doomed? What can/should I do to attempt preventing T2D?

Edit: also, is there any genetic testing I can get done to find out more?

[incredibissell](#)

Jason here. As Mark said only he is a physician so we will be focusing on our research here; talking to your doctor is always the best course of action for personal advice.

With respect to your question about genetic testing: one of the things our work does show (but which to be honest has been apparent for some time now) is that genetic tests to predict risk for T2D are really in their infancy and don't have as good predictive power as models based on traditional risk factors like age and weight.

Hi everyone. Can you guys explain why there is a higher tendency for people of South Asian origin to get Type 2 diabetes later in their life?

[sarkasm](#)

Mark here. Important qn.

Cant give a definitive answer but some of the clues

- very different distribution of fat between folks from S Asia and European. For same BMI, someone from S Asia will typically have a lot more central (visceral) fat, which is as you know more metabolically impactful
- many of the pops with large rates of diabetes now have gone through rapid demographic shifts. Plenty of evidence that its a particularly diabetogenic combination to be born small (due to limited fetal nutrition) and then put on weight in adulthood, so this may be the consequence of some of the big economic changes for many in India and china over a generation
- there may well also be genetic differences that are contributing. We have seen a few variants popping up that are population "specific" but these dont seem yet to be enough to explain the differences in prevalence between major populations.

very much something we are working on at the moment, and there are big efforts to expand the amount of genetic information re T2D in S Asians. Stay tuned. Mark

It would be helpful if you specify Type 2 Diabetes on your title, I am a Type 1 (LADA) with some questions on genetics and I'm seeing the focus of your research is on Type 2.

Makes me wonder if a lot of the current confusion in the medical community when it comes to Type 1, 1.5 LADA, MODY and Type 2 is in part due to the field always lumping us all under a general

"Diabetes" umbrella.

[LOUF72](#)

Mike: Something we as geneticists focus on is definition of phenotype and deciding when to lump conditions together and when to split. This splitting (leading to more homogeneous but smaller) data subsets is actually quite important in our diabetes genetics work and generally increases the power of our statistical analyses. Nonetheless, there are overlaps in the genes involved in the different forms of diabetes, notably between T2D and MODY. For example, in our paper that just appeared in Nature, we described a common variant in east Asians in the gene PAX4 that predisposes to T2D; mutations in that same gene cause MODY.

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[LOUF72](#)

Mike: You are totally right. We are seeing if we can change the general title. We did have T2D everywhere else but not in that top level title. Thanks for the suggestion.

1. Why does Gestation Diabetes give the child a higher chance of developing diabetes?

-One of my kids has a higher risk for diabetes because of GD. Is the risk mostly for people who are overweight? Or could he develop it as a child? I'm confused on how this works.

1. My sister has developed type 2. Can it cause infertility?

[Lady_Generic](#)

Hi there Mark here. Interesting questions.

1: GDM. Several factors in play. For one there's the simple genetics. GDM is associated iwth an increased risk of T2D in later life, and the genetic risk factors are likely much the same. So in the same way as any parent or close relative with diaebtes will increase risk of diabetes through shared genetics, there will be an increased risk in the offspring (but only an increased risk, not definite diabetes). There does seem to be an additional factor though in the case of a mother who is diabetic during the pregnancy which further increases the risk of diabetes in the offspring of that pregnancy. Mechanism really isnt clear. Perhaps the exposure of the fetus' developing pancreas to high glucose levels coming across the placenta has some long term impact on islet number or function that translates into a higher risk of diabetes in later life. This is part of the reason why we try and manage diabetes during pregnacny as strictly as possible. AS for the age of diabetes.....mostly this would be about diabetes onsetting in later life.
2: yes there can be infertility mostly associated w Polycystic ovary syndrome which is quite closely realted to type 2 diabetes in many ways (folks with one are at increased risk of the other)

Sorry for the consecutive questions, but I believe this are all somewhat related. An answer to any question would greatly be appreciated :)

1. With the question of missing heritability ever present in GWAS studies, do you think this study could

help shed light on the need for understanding intronic variants and transgenerational epigenetic inheritance (and in particular the frequency of DNA methylation/histone modification)?

2. Since you did whole exome sequencing, do you believe a study like this has potential to shed light on the genetic questions regarding missing heritability?
3. Are there any efforts to use your genetic linkage data for T2D population studies to assess disease risk for environment in the future?
4. In regards to personal opinion, does anyone on your team have a large amount of "optimism" for particular post-GWAS analysis ?

[MetaButtMethane](#)

mark here. lots of qns. Some quick answers.

1. the more studies we do, the less and less "missing" heritability there seems to be. Recent studies for BMI show that in fact most of the missing heritability can be found by just including a very long tail of genetic effects of individually small effect but cumulatively large impact. See the work by peter Visscher if you want to read more esp his recent paper in Nature Genetics. For technical reasons, those studies are not so easy to do for T2D than for a continuous trait like BMI but no reason to suspect that its any different. TGEI is a whole other matter (very controversial, wont get to that today)
2. yes, because we could take a deeper dive into the exomes we could really parse out the relative contributions of common and lower frequency variants there, and get a glimpse about how that might play out across the genome. Mostly consistent with (1) above, that if you look down the list of common variant signals you can explain a good amount of the overall heritability.
3. Yes, very much so. Thought its been tough to turn these anonymous GWAS hits into biology, that is changing fast. Not least because we have spent a lot of tiem and effort collecitng genomic data from key tissues (expression, chromatin state etc) and that is helping us work out what the variants we have discovered actually do, and the pathways and networks they perturb. Things are really accelerating in this regard. Of the 100 or so GWAS signals for T2D i would say we have a decent idea of what is going on (the tissues/mechanisms/genes involved) at around 40%. That's a really good start to thinking about new ways of treating and preventing the disease

How much of the hidden heritabilty for diabetes and obesity can accounted for by the gut microbiome, which is mostly transfered maternally, and the effects of child rearing, transfered from both parents?

[cvbnm890](#)

mark here. great qn. very topical. those studies being done now, no answers yet. see answer to another post i made about microbiome about 30mins back....

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Jason here. Alongside this paper we also published a review which gives a sense as to what (at least I) think to be the most interesting directions

<http://www.nature.com/nrg/journal/vaop/ncurrent/abs/nrg.2016.56.html>)

In short, I think insights like SLC30A8 and PPARG (referenced in another post) show that there are a

lot of insights in these data, but you have to dig for them. Systematically characterizing rare variants in laboratory assays with new technologies like CRISPR are a particularly cool direction IMO (see <http://www.ncbi.nlm.nih.gov/pubmed/25157153>)

My father developed type 2 around 12 years after I was born. Is this a sign that I am more likely to develop diabetes?

[giordam90](#)

Andrew: a family history of diabetes is associated with increased risk of the disease. However, type 2 diabetes involves many genetic and environmental risk factors, so the fact that your father has the disease does not mean that you will develop the disease for certain.

I have a mitochondrial mutation, A3243G. As a result I am diabetic, but currently so mild I am not on any medication. Other family members are not so lucky. We have all been diagnosed and treated as type 2, though I know that many people with A3243G are diagnosed with type 1.

I wondered how much mitochondrial mutations factored into type 2 diabetes, and if it was a higher number than previously thought.

[apricotmuffins](#)

Hi Mark here. Brief response. Yes 3243 is very much implicated in diabetes but as you probably know there's quite an element of chance about how much of the variant form of 3243 ends up in each individual (and in each tissue in each individual). That goes a long way to explaining the differences in the clinical features seen in the individuals from the same pedigree. That's a particular feature of mitochondrial mutations. Quite a lot of work done to look for other mt variants that might have a role in diabetes risk. About 15y ago there was a flurry of excitement about a variant at position 16189 in the mitochondrial DNA sequence but that really hasn't panned out (in that larger studies failed to corroborate the findings). A few quite large studies have now looked hard and failed to find any other clear signals in the mitochondrial sequence that are implicated in Type 2 diabetes. Surprise really given that there's a good bit of evidence that mitochondrial function is relevant.

Why do East Asians suffer from diabetes at lower BMIs than blacks or whites?

Why does bariatric surgery put diabetes in remission even if someone is still fat?

What is your opinion of the Newcastle diet as a diabetes cure?

[Five Decades](#)

Mark here - i just answered a couple of the qns here in a post i just made. So you might want to search that out.

In diabetics, do cells that have insulin-independent transporters still take up blood glucose since the cells that contain insulin-dependent transporters no longer do? If so, why is there still high blood glucose levels if the insulin-independent transporters still function? Wouldn't the concentration of the glucose outside of the cell be more than inside, driving it to move inside of those cells via facilitated diffusion?

[FivePillars114](#)

Jason here. This isn't fully understood; people become insulin resistance presumably for many reasons, but it isn't an either or. Even if cells take up glucose, they may do so less effectively (for example, less transporters may make it to the surface of the cell in response to insulin). Most people who are insulin resistant aren't yet diabetic however, and it's typically the failure of the beta-cells to produce enough insulin (in the face of this resistance) that causes them to develop T2D

Have you identified anything specific within the Hispanic community that genetically predisposed them to diabetes?

I did some research in one of my classes in university on that topic as a Political Science student, so I didn't get too deep into the genetics, but I'm interested if you all have identified anything in that regard.

[adriens95](#)

Jason here. See <http://www.nature.com/nature/journal/v506/n7486/full/nature12828.html> and <http://www.ncbi.nlm.nih.gov/pubmed/24915262> for some examples.

Hi Mark,

It's very nice to know that you're holding an AUA! I'm interested in your latest paper. Sorry that I'm quite new to the field, so please bear with me if I asked the wrong questions...

How would you compare the results obtained from WGAS and EWAS with those from GCTA? Are the findings congruent? I read from the abstract that seems like the missing heritability cannot be explained by rare variants, and most common variants were already discovered by previous GWAS. What else could explain the missing heritability, and what can you do to look for it?

[dillyia](#)

Jason here. I think this study is very complementary to those from GCTA. Our study suggests rare variants of high impact have a minimal contribution to T2D heritability, even while we find many common variants associated. The GCTA papers show that "missing heritability" can be explained in large part by common variants tagged by GWAS.

In my opinion, most of the remaining "missing heritability" is likely due to ever more common variants of weaker and weaker effect, as well as many other variants of all frequencies (but with common variants contributing the bulk, simply because their frequencies are so much greater)

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[dillyia](#)

Andrew: these are really good questions! I think it is fair to say that there are unlikely to be rare variants with a big effect on type 2 diabetes. However, there may be rare variants with more modest effects on the disease that we have not yet been able to identify, even with the tens of thousands of

samples we've included in this study. So I think part of the missing heritability will be made up of both common and rare variants of small effect that we have not found yet.

People from a certain area and especially family members tend to have similar genes, but also share a common culture which can include lifestyle choices that affects one predisposition for diabetes. When doing your research how do you tease apart these two? As in how do you know if a particular gene increases/decreases risk or if people who happen to have that gene also happen to belong to a certain group that does such and such and that is what increases/decreases risk?

[perib](#)

Jason here. Confounding between a person's ancestry and their T2D risk is a key challenge in this sort of study; fortunately genetic information allows us to actually estimate ancestry and control for it (as best we can). Controlling for different lifestyle choices is harder, and we typically need to do that at the time the study is designed (such as controlling for people's age, BMI, and other known risk factors)

So I'm not sure how related this is to this specific project, but I've never gotten an answer I really understood. What is the link between diabetes and foot problems?

I know there is a high correlation of diabetics with things like gout and amputation of feet/legs, and my dad (type 2 fully insulin dependant diabetic) says that the fact I have poor circulation in my feet means I'll probably develop diabetes too.

[spekter299](#)

Andrew: there are many complications that can occur as a result of type 2 diabetes, some of which might lead to a need for amputation of limbs. However, these are as a consequence of the disease, and not a risk factor for type 2 diabetes in themselves. The fact that you have poor circulation in your feet does not mean you will get type 2 diabetes.

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[spekter299](#)

Jason here. It's the other way around. Most of the complications of T2D are related to the blood vessels, so neuropathy (nerve damage in the hands or feet) is a common complication (in addition to other vascular disorders like stroke, heart attack, kidney failure, and retinopathy). So T2D causes nerve damage, not vice versa

I got gestational diabetes when pregnant, but it never went away. I am not overweight, and neither are most people in my family, but for some reason we all have diabetes or pre-diabetes. People are always surprised when I tell them I take metformin. They say that I must be mistaken and have type 1 not type 2 diabetes because of how I look and my fairly healthy lifestyle. I tend to say, "it's type 2, but must be genetic." What's going on here? Should I be concerned for my children (who are currently 2 and 4)?

[skiballerina](#)

Jason here. As mentioned above T2D is a combination of genetic and environmental risk factors (30-70% of your risk is determined by your genes). There are definitely young, thin people who develop diabetes (both T2D as well as other clinical conditions that are similar to but distinct from T2D). A very active research area is seeing whether we can come up with better means of assessing genetic risk; right now though these are not as accurate as traditional risk models

I hear quite a few people say they reversed their diabetes by using some fad diet (raw veganism, half veganism, paleo, juicing, etc.). Is it actually possible to reverse diabetes? Or just to control it?

[itawtgtwoms](#)

Jason here. I'm not a clinician, but to my knowledge there are no proven means to actually reverse diabetes.

I know someone who has weighed over 300lbs for decades and has even weighed over 500lbs for extended periods of time. This person does not have diabetes, but is said to have "pre-diabetes." First, what's the difference between pre-diabetes and diabetes? Is it possible that what's considered pre-diabetes are actually separate issues that often occur alongside diabetes? To what level could genetic, lifestyle, or dietary factors determine whether someone develops diabetes?

[deadowl](#)

Jason here. Pre-diabetes is a condition of elevated glucose levels that can commonly progress to T2D. For example, fasting glucose > 125 is a classification for T2D while 100-125 is pre-diabetes; there are similar criteria for 2hr glucose and A1C. Lifestyle interventions (diet and exercise) are the best proven ways to delay progression to T2D (<http://www.nejm.org/doi/full/10.1056/NEJMoa012512#t=article>) although metformin is also commonly used.

Are there specific pathways affected by or linked to diabetes? What is the most common problem you face in your research? Do you work on the development of drugs to combat diabetes? How do you test those drugs? Are there specific regulations that impede your ability to conduct your research?

These can be answered succinctly if need be and I'll do further research based on your answers.

But I'd love some long explanations :)

[Parallelbhe](#)

Jason here. Two of the most common pathways that pop up from studies of T2D (and related diseases) are genes that act through the beta-cell and affect insulin secretion, as well as insulin signaling (this review I wrote a few months back has a figure illustrating some of them (<http://www.nature.com/nrendo/journal/v12/n7/abs/nrendo.2016.50.html>)). Of course more specific pathways are the holy grail of our sort of research, and things like zinc transport into beta-cells and cholesterol efflux from the liver are two more recent ones that have popped up.

Most common problem: genetics gives you a sign post into a region of the genome that affects T2D risk but doesn't tell you why; figuring out why is enormously hard and can take years.

We don't work specifically to develop drugs but we are involved heavily in the AMP-T2D consortium, which aims to forge partnerships between academics and the drug industry to help design better drugs

(<https://www.nih.gov/research-training/accelerating-medicines-partnership-amp/type-2-diabetes>).

What exactly is the relationship between heart disease and diabetes? Does the onset of type 2 diabetes result in heart disease or do high cholesterol and triglycerides result in diabetes? Also, a number of studies about diets and diabetes quote China. Why doesn't anyone study India, where the diet is largely vegetarian, but there is a high prevalence of diabetes and heart disease?

[halibattu](#)

Jason here. Cholesterol levels are the dominant determinant of heart disease. However, people with T2D are more likely to develop heart disease (I think like a 2-fold elevated risk), and this risk seems in excess of any effects due to elevated lipid levels from T2D.

There are some studies of T2D genetics in India. In fact about 1000 of the individuals in our study were of Asian descent.

Who are you most likely to inherit a propensity for diabetes from? Your mum or dad? Pretty much everyone in my dad's family has had diabetes, including him. My aunt has 2 boys that have seem to dodged the bullet, but of my cousins kid is diabetic...any thoughts or theories on the patterns of inheriting a propensity for diabetes?

[tzotzchoj](#)

Hi - Mark here. Quick answer.

Most of the evidence suggests that people with diabetes slightly more often say that their mother had diabetes than their father. But of course there may be lots of reasons for that in some of the studies (fathers more often leave home, die in wars etc, mothers live longer and so have more time to develop diabetes etc). Genetic transmission should be equally between mothers and fathers (unless mitochondrial variants matter, and not much evidence they do).

But there a couple of other factors that might push the maternal rate up a bit. there seems a specific effect of being born from a diabetic uterus (ie mother had diabetes during pregnancy) that increases diabetes in the offspring a bit. So that may be part of the story, and might push up maternal transmission a little.

But its not a big difference.

Thx Mark

My grandma and almost all of her siblings ended up with type 2 diabetes. Great grandma, and great great grandma also had the affliction. My mom is in the clear so far. What are my chances of developing the disorder?

[inkoDe](#)

Andrew: unfortunately, we can't predict your risk of developing type 2 diabetes with certainty. A family history of type 2 diabetes is associated with increased risk that you will develop the disease. However, there are many genetic and environmental risk factors for the disease, so the fact that so many relatives have type 2 diabetes does not mean you will develop the disease for sure.

Hi,

More a Personal question but what did you study to get where you are? Are you biologists? I am thinking about studying pharmaceuticals Thanks

[aminem96](#)

Mike: My undergraduate training was in mathematics. I like math and am even reasonably good at it, but did not see a career path that excited me. I almost decided to pursue a law degree, but was encouraged as I was finishing college to think of a career combining math and biology. I did not jump on the idea initially -- I had not taken a course in biology since the 7th grade -- but eventually decided that this might be a way to keep doing math and do something I would find exciting. A few months later, reading a biology book, when I got to the chapter on genetics, I WAS excited; it was probability, and I like probability! It still took me a while to decide specifically to pursue the path I did, but those were key moments.