Science AMA Series: We're researchers at the NNF Center for Basic Metabolic Research, University of Copenhagen. We recently published a study showing that obesity may be inherited through epigenetic mo

NNF$_{C}enter^{1}andr/ScienceAMAs^{1}$

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Abstract

Hello Reddit! We are Ida Donkin, Soetkin Versteyhe, Lars R. Ingerslev, and Romain Barrès from the Novo Nordisk Foundation Center for Basic Metabolic Research. We recently published a study that shows that sperm from obese men carry a distinct epigenetic signature compared to lean men, in particular at genes controlling brain development and function. In addition, we also looked at gastric bypass patients before and after surgery, and found that the sperm methylome is remodeled notably at gene regions implicated in the central control of appetite. Please Ask Us Anything! We will start answering questions at 1 pm EST (19:00 CET). EDIT 3.20 PM EST: Thank you so much for all the great questions! We're signing off now, but we'll check in again tomorrow for a few follow-up questions. Again, thanks guys! ANOTHER EDIT: The story behind the AMA here: http://www.museion.ku.dk/2015/12/reddit-science-ama/ Links: The actual paper: http://www.cell.com/pb-assets/journals/research/cell-metabolism/on/cmet1935_r.pdf NY Times http://www.nytimes.com/2015/12/08/science/parents-may-pass-down-more-than-just-genes-study-suggests.html The Guardian http://www.theguardian.com/science/2015/dec/03/overweight-men-may-pass-genetic-obesity-risk-to-their-children Our research group: http://metabol.ku.dk/research/section-for-integrative-physiology/environmental-epigenetics/

the WINNOWER

REDDIT

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NNF_CENTER R/SCIENCE

ABSTRACT

Hello Reddit!
We are Ida Donkin, Soetkin Versteyhe, Lars R. Ingerslev, and Romain Barrès from the Novo Nordisk Foundation Center for Basic Metabolic Research.
We recently published a study that shows that sperm from obese men carry a distinct epigenetic signature compared to lean men, in particular at genes controlling brain development and function. In addition, we also looked at gastric bypass patients before and after surgery, and found that the sperm methylome is remodeled notably at gene regions implicated in the central control of appetite.
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Links: The actual paper: http://www.cell.com/pb-assets/journals/research/cell-metabolism/on/cmet1935_r.pdf
NY Times http://www.nytimes.com/2015/12/08/science/parents-may-pass-down-more-than-just-genes-study-suggests.html The Guardian http://www.theguardian.com/science/2015/dec/03/overweight-men-may-pass-genetic-obesity-risk-to-their-children
Our research group: http://metabol.ku.dk/research/section-for-integrative-physiology/environmental-epigenetics/

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WRITE A REVIEW

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Would there be a genetic benefit to getting in shape and incredibly healthy just prior to passing your genes along and then returning to obesity once your done having children?

smpl-jax

Romain Barrès: We don't know yet. We need to understand which of the sperm marks that are changed in obesity are transferred to the child before answering this question

Does this mean that if a person with a predisposition to being obese, were to spend their life dieting and exercising correctly, would the epigenetic signature change for the next set of offspring?

RandomBellend

Ida Donkin: We know for certain that the epigenetic signature of human sperm cells changes if losing weight after bariatric surgery, or exercising (data not published yet), but what we still lack to investigate

showing that obesity may be inherited through epigenetic mo, *The Winnower* 2:e145009.95401 , 2015 , DOI: 10.15200/winn.145009.95401

is whether these changed epigenetic patterns of the sperm cells also affects the health of the next generation. We have done studies in rodents showing us that a changed epigenetic pattern of the sperm cells will lead to a changed health of the next generations. We hypothesise that this will be so for humans as well, but we do not know this for sure yet. This is something we currently investigate.

Hypothetical question here. Let's say someone is 5'8", 300+ lbs and never exercises. This person gets motivated by someone he cares for and they want to have a baby. Following a disciplined eating and exercising regimen, how long would it take for this person's sperm to rid itself of the "distinct epigenetic signature" so as not to pass along this obese trait? Is there a certain target height to weight ratio?

Dickwagger

Ida Donkin: We are not sure how long it takes to get rid of the epigenetic pattern in your sperm cell caused by obesity, but we know that we can change - at least parts - of the epigenetic patterns within two weeks, as this was the time separating the two first sperm samples received from the study participants undergoing bariatric surgery (1 week before surgery and 1 week after surgery). What we don't know yet is whether you are able to change the complete epigenetic pattern by losing weight, or whether some parts of the epigenetic patterns associating with obesity may be permanent (or at least less susceptible to changes in our lifestyle). We do not have a certain target height to weight ratio, but would encourage people to aim for a 'normal' BMI which is within 18,5-25.

Since your institution is involved in metabolic research-- have you looked at all in the role of O-glcnac in the epigenetic changes that are taking a place? O-glcnac has been called a 'total metabolic sensor' and patterns of O-glcnac are altered in a state like diabetes. Additionally O-glcnac is part of the histone code

http://www.ncbi.nlm.nih.gov/pubmed/21045127

And has been shown to be involved in DNA methylation processes and higher order chromatin structure:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3590992/

http://www.ncbi.nlm.nih.gov/pubmed/22522719

It would be interesting to see if a metabolite like UDP-glcnac (the precursor for O-glcnac) and the metabolic flux of metabolites leading up to UDP-glcnac are altered in obese people and contribute to the epigentic changes observed here.

xSialicAcidx

Soetkin Versteyhe: That is an interesting question - we have however not looked at it.

It has been shown that pesticides such as DDT can cause changes in sperm resulting in generational obesity: http://www.ncbi.nlm.nih.gov/pubmed/24228800 -- are you seeing other potential causes?

TheYogi

Romain Barrès: That is an interesting paper. What puzzles me is that many stressors (pesticides, famine, psychological stress) converge to a metabolic (obesity, glucose intolerance) phenotype transmitted transgenerationally. The current hypothesis, to answer your question, is that stress hormones triggers the transgenerational phenomenon. i.e. stress hormone levels could be the cause of

the phenomenon.

From what I understand (not much but I do understand something) those epigenetics mean - a way that an offspring will inherit traits from their parents, Not in the form of the parent's dna but from the other components(all the things inside the egg/sperm that are not dna)...

Also: If I recall correctly, all the female eggs are created in the early stages of the female's life. Male sperms, on the other hand, are created continuously throughout their life.

And the question is: Can we assume that the female's obesity level will not impact the child via epigenetics (because the eggs are already created when the female starts to develop obesity so the female body state will not alter the components of the already formed egg) But the male obesity level Will impact the child via epigenetics (because the male is already obese when the sperm is being created so the sperm is probably created differently than when the male is not obese)

I might have overcomplicated the question but I hope the point gets across.

Also sorry for the bad English, it's not my primary language.

IL_is_not_ItaLy

Lars R. Ingerslev: Epigenetics is indeed a way to inherit traits that are not encoded in the DNA, small non-coding RNAs are not part of the DNA, histone modifications modify the accessibility of the DNA and methylation is a modification of the DNA that does not change the genomic sequence. Secondly: It is very well established that the weight of the mother will affect the offspring. The embryo from an obese mother will develop in the uterus of an obese mother and will affect the child. Figuring out what is caused by epigenetics of the egg, and what is caused by in utero development would be difficult to do in an ethical manner. There is nothing to suggest that the egg is less susceptible to change than the sperm cell, but eggs are MUCH more difficult to obtain than sperm which is a practical reason it is less studied.

Very interesting study. Aside from this,what are the most interesting or promising epigenetic findings of the past 5 years?

Warrior77777

Ida Donkin: If we stay within the field of epigenetic inheritance (as the field of 'epigenetics' is enormously big), I would say that some of the most important findings are the following:

Dias, B. G. et al (2014): Parental olfactory experience influences behavior and neural structure in subsequent generations. http://doi.org/10.1038/nn.3594 If you repeatedly expose a male mice to electric shocks simultaneously with the smell of acetone he would naturally, after a while, develop a shock response just when experiencing the pure smell of the acetone. Surprisingly, his sperm cells will change their epigenetic pattern in response to this, and his children will also react with a stress response when smelling acetone - telling us that the experience of electric shock has been transferred forward to the next generation. This study tells us that it is the sperm cells transferring this response to the next generation, as In Vitro fertilization using the male mice's sperm could replicate the transfer of the stress response to the next generation.

Gapp, K. et al (2014). Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. http://dx.doi.org/10.1038/nn.3695 RNAs in mice sperm can transfer an epigenetic memory of a traumatic experience to the next generation, changing the next generation's behaviour and metabolic health.

Barrès, R. et al (2012) Acute exercise remodels promoter methylation in human skeletal muscle.. Acute exercise remodels promoter methylation in human skeletal muscle. http://dx.doi.org/10.1016/j.cmet.2012.01.001 This study tells us that lifestyle interventions can dynamically change the epigenetic patterns in our somatic cells. In fact, they change just within a few minutes following a short session of exercise.

What is the "cutoff point" for this change to happen? I was slightly overweight when my second daughter was conceived, she is due in two weeks. While I wasn't obese by any means I am still worried when seeing this headline.

Great work by the way, I never even considered that sperm could genetically change. This could have implications beyond the obese thing.

Jts20

Soetkin Versteyhe: The epigenetic changes we found happened in the sperm of men with a BMI of at least 30. We do not know at this point whether slight overweight can induce epigenetic changes in sperm as well. In addition, we did not study the offspring of the obese men in our study, so we do not know yet whether the epigenetic changes we find in sperm will lead to a change of health in the offspring. We know from animal studies that certain epigenetic marks can be transferred to the next generation and that nutritional status of fathers can affect health of the offspring. We believe that specific epigenetic marks of obesity will be retained in the offspring and affect their health.

Were histone modifications also altered?

Jengis_Roundstone

Lars R. Ingerslev: Measuring histone modifications were originally part of the project, but the vast majority of the genome is bound by protamines (about 98% protamine and 2% histones according to our study, which is in the same range as what has previously been reported). We did not have enough DNA to reliably determine histone modifications and could only measure histone localization. We did find that the histone-bound regions were located in promoters of genes related to development, especially neuronal development.

What is the proposed mechanism by which methylation patterns are actually altered? Are there enzymes that respond to body chemistry in a specifc way that lead to these consistent patterns?

Jengis_Roundstone

Romain Barrès: Very interesting question. We and others have found that saturated fat or inflammatory cytokines can change the epigenetic status of a cell. We can only speculate that these factors could be involved in “shaping” the methylation of sperm cells.

How could the extent to which these gametic epigenetic changes in obese men influence the metabolic profile of their offspring be controlled for to discover the specific nature of such inherited metabolism?

Would a mice model be ideal for future study?

willonz

Lars and Soetkin: Looking at how the changes affect the offspring is indeed the next step. We are currently collecting cord blood from newborns and the sperm of their obese fathers to see which changes persist in the next generation. In addition, a collaborator of ours is currently in the process of publishing a paper on obese rats and the epigenetic changes in their sperm. In mice, paternal obesity alters microRNA expression in sperm (Fullston, T., Ohlsson Teague, E. M. C., Palmer, N. O., DeBlasio, M. J., Mitchell, M., Corbett, M., et al. (2013). Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete penetrance to the F2 generation and alters the transcriptional profile of testis and sperm microRNA content. The FASEB Journal, 27(10), 4226–4243. http://doi.org/10.1096/fj.12-224048).

How do you feel this research helps/hinders the stigma of obesity?

HornOfDagoth

Romain Barrès: Good question. We need to know if the epigenetic factors are POSITIVELY or NEGATIVELY affecting the health/appetite of the offspring. Maybe the changes we see in obesity are transmitted to children and DECREASE appetite. Maybe. And that would mean that epigenetic transmission is a GOOD thing that could be overwritten by environmental factors in the life of the offspring. Back to your question: our research could hinder the stigma of obesity IF the EPIGENETIC transmission is going towards a better appetite control of obesity in the offspring…

What other lifestyle affected traits do you suspect would be worth studying for similar epigenetic switches? What are future areas of study?

pricklycitrus

Soetkin Versteyhe: A recent study has shown DNA methylation changes in human sperm after 3 months of exercise training. Smoking has also been shown to alter microRNA expression in human sperm. Future areas of study are any common environmental factor affecting humans. We are currently working on trying to link epigenetic patterns in sperm cells of obese men with the epigenetic patterns in the cord blood cells of their offspring.

Going through the study more in depth - I really appreciate the presentation of the study. The significant differences in methylation patterns of obesity linked genes (FTO, MCR4) are very obvious. I also appreciate the genetically similar population (Danish caucasian men) which have been well studied in regards to lifestyle related disease and genetics. Are there plans for study looking at obese men and women (at conception) vs non-obese and common health markers at birth e.g. HOMA B, HOMA IR, birth-weight and longitudinal follow ups?

Mangosteener

Ida Donkin: Thank you for your kind reply. We are currently investigating pregnant couples and matching up the parent's epigenetic signature to the epigenetic signature of the newborn's stem cells, to see exactly what patterns are being transferred to potentially affect the health of the offspring. As we have included couples with fathers who are either of normal weight or obese, this will hopefully tells us: 1) does the epigenetic pattern of the newborn's stem cells (taken from the cord blood at birth) differ if the dad is obese as compared to if he is lean? 2) exactly what patterns are being transferred from parents to the new-born baby. We are currently not planning any follow-up studies on the actual implication of the health of the newborn.

Your graphical abstract hinted at the idea that the epigenetic alterations could impact brain development relevant to homeostasis/food choices but the text did not seem to address this in detail. Can you expand more specifically on this? What brain regions or processes would you expect to be effected and why? Nice paper, us fathers don't get enough attention and credit for programming obesity in offspring!

jerodras

Ida Donkin: Thank you for your question. Yes, we saw several genes known to modulate the central regulation of appetite and food behaviour that was epigenetically regulated in the sperm cells after the weight loss after bariatric surgery. Moreover, we saw a significant overlap of genes epigenetically regulated in the sperm cells of obese males overlapping with the findings from a different study investigating epigenetically regulated genes in sperm cells from fathers having children diagnosed with autism (Feinberg et al, 2015: http://ije.oxfordjournals.org/content/44/4/1199.long). Knowing that obese dad's have a higher risk of having children who will be diagnosed with autism, this tells us that the epigenetic patterns observed in the sperm of obese men may likely regulate the brain development and thereby the eating behavior of the next generation.

from lean, normal-glucosetolerant(me-dian body mass index, BMI, of 22.9, referred to as ''Lean'') and obese, glucose intolerant men (median BMI of 31.8, referred to as ''Obese''

Why do you use BMI when you study obesity? Why aren't you talking in body fat % and hip-waist ratio? I've seen mention of both in the study, but you keep correlating it with BMI instead. For all we know, if we use BMI as a factor, it'll mean that a body builder would be in the same "bucket" as someone who is simply obese. Doesn't that mischaracterize your study, or is that the case, do body builders have the same issues?

I suppose that you, indeed, took men with a surplus of adipose tissue, but, for all we know, they could also have been body builders, since all you are using for correlation is BMI.

Why not use a more appropriate measure of body fat?

MonsterBlash

Soetkin Versteyhe: Thank you for the good question. We used BMI because WHO's definition of obesity is based on BMI cutoffs. That been said, we did make sure that our study did not include 'body builder' phenotypes. The obese men did not exercise more than twice a week and they showed increased body fat percentages and increased waist/hip circumference.

What a fascinating study. Studying sperm as opposed to oocytes in the context of metabolic traits has been an exciting field of research since mitochondria are maternally inherited.

Can you speculate as to whether or not the obesity-regulated spermatozoa eipgenome could be manipulating mitochondrial function through nuclear-mitochondrial cross-talk?

Dr_Boner_PhD

Romain Barrès: Thank you for these nice words and very interesting question. One way to answer your question: epidemiological studies shows a sex-specific transmission of nutritional stress (pembrey 2006), meaning that men's nutrition affects the health of their sons, but not daughters. This observation would go AGAINST your hypothesis that men epigenome (sperm) affect the epigenome of a maternal lineage.

Assuming epigenetic signature can change with the change in bodyweight, does it make a difference if the weight loss was due to say, bariatric surgery, low carb diet, low fat diet or due to exercise.

In other words, which weight loss method has the highest likelihood of changing the epigenetic signature?

dum_dum_dummm

Ida Donkin: Hi, thanks a lot for your questions. We are not sure about this. After a bariatric surgery, a lot of changes will happen to the individual. One thing will for sure be a change of diet, but he may also exercise more, quit smoking, drink less alcohol, socialize more, etc, and we do not know which of these factors (or whether it is all of them in combination) that are responsible for the changes seen in the sperm cells. We also know that several weeks of intense exercise in males previously of unfit state can change the epigenetic patterns (data to published yet), but once again we are unsure whether the changes observed are due to the exercise itself or other lifestyle-related changes they may have initiated in the same period. We are currently investigating exactly what factors are creating the changed epigenetic factors in the sperm cells seen after the bariatric surgery, but it will probably take us a few more years before we can answer this with certainty.

Assuming 72 days is the average time for new sperm to be created, would significant weight loss for 72 days be sufficient to change the epigenetic signature ?

dum_dum_dummm

Soetkin Versteyhe: We see DNA methylation changes in sperm 1 week after a gastric bypass operation, so our data suggest that epigenetic marks can be altered at the late stages of sperm development.

But why has my younger sister always been heavier/chunkier since birth almost, and I have naturally always been thinner? My father is thin. My mother is the one who gained weight after she had me. I guess what I'm saying is, are there plans to study the mothers role?

lifesquixotic

Soetkin Versteyhe: That is a tough question. Many factors can affect BMI of offspring. Obesity in the mother during pregnancy is known to be able to affect the health of her offspring.

Does epigenics explain why obese people eat far more food than their body needs, thus causing them to gain weight or do obese people have some kind of special metabolism that would allow them to be a normal weight on fewer calories than average so their weight is based on some ability to store fat far more efficiently than average?

Eriamjh1138

Ida Donkin: Hi. Epigenetics may for sure be part of the explanation, but most likely there will be several different factors explaining it, such as a mix of epigenetics, genetics, culture, upbringing, socioeconomic factors etc. But.. that being said, once obese your whole body's metabolism will change, making it more difficult to lose weight than if you were lean. So, yes, once you have become obese your metabolism of fat storage/fat utilization will definitely change.

The mechanism by which histone modification is thought to lead to phenotypic changes is by altering accessibility to certain regions of DNA and therefore altering gene expression. Is there a model for how DNA methylation leads to phenotypic change?

Elandiga_Varg

Lars R. Ingerslev: Yes although the link is less clear-cut, DNA methylation in promoter regions often correlate with a decreased transcription by hindering the binding of transcription factors. Methylation in gene bodies is weakly correlated to increased transcription, possibly by opening up the DNA. In other genomic regions it depends on the function of the region.

How could a similar epigenetic switch operate through the mother? I.E. can egg be effected in her lifetime?

pricklycitrus

Lars R. Ingerslev: There is nothing to suggest that the egg is less susceptible to change than the sperm cell, but eggs are MUCH more difficult to obtain than sperm which is a practical reason it is less studied.

Could epigenetics explain other demographic trends? Such as gun violence in the USA?

Speiderman

Romain Barrès: I really don't think gun violence can be explained by epigenetic inheritance. Few studies suggest that response to fear are transmitted through sperm in mice, but to my appreciation, other socioeconomic factors explain increased violence in our developed countries.

Can you confirm that even if people are genetically predisposed to obesity, they still can absolutely control their weight through diet and exercise? That genetic predisposition is not a sentence to being obese?

chicklet2011

Ida Donkin: Hi, thanks a lot for your questions. Most of the genetic mutations identified so far associated to the development of obesity has such a small 'effect-size' (meaning that the change in BMI this genetic mutation is actually responsible for is very, very small) that you will for sure be able to overrule the genetic predisposition to obesity by diet and exercise. Not saying that this is easy though, once obese it can be very difficult to lose weight again as your whole body's metabolism changes. However, a few (very few) of the genetic mutations associated to obesity does have a rather large effect-size. As an example, a mutation in the leptin gene can create morbid obesity already in the early years of one's life - and this specific mutation is very difficult to overcome, even with strenuous exercise and very strict diets.

Approximately how long does it take for epigenetic modifications to manifest in noticeable amounts? Does it take years for a certain amount of modifications to accumulate? Or can these things happen in a matter of days?

ViperSRT3g

Ida Donkin: In our study we saw that just two weeks (comparing sperm samples from the same individual 1 week before and 1 week after the bariatric surgery) were enough to dramatically change the epigenetic patterns of the sperm cells. In other studies, we have shown that just a few minutes of exercise were enough to change the DNA methylation patterns of muscle cells - and that the gene expression of the exact same genes changed shortly afterwards (Barres et al, Cell Metabolism, 2012 - http://dx.doi.org/10.1016/j.cmet.2012.01.001)

"We recently published a study that shows that sperm from obese men carry a distinct epigenetic signature compared to lean men, in particular at genes controlling brain development and function."

-- Can you please be a little more specific in what brain development and functions are expected to be altered? For instance, is the progeny expected to be developmentally delayed? Or will they have less impulse control, especially in regards to food (though this could be viewed as a nurturing issue)? Essentially what's the overall expected outcomes for the resulting child?

mcdunna4

Soetkin Versteyhe: Our data do not show developmental delay. We can see changes at different genes involved in nervous system development and appetite control.

So epigenetic modification secondary to starvation during pregnancy, or other food intake factors of prior generation(s), with a small, unpredictable effect, or is it a statistically significant effect with regard to the null hypothesis? In turn, would the male children in these circumstances have a greater probability of obesity. I am thinking specifically of the Dutch Hunger Winter.

maileek

Lars R. Ingerslev: I am a little unclear, are you questioning if starvation during pregnancy has a greater effect on the embryo than epigenetic changes brought about by obesity? In many models, including humans, severe caloric restriction during pregnancy leads to an increased risk of obesity later in life. Whether this effect is stronger than other environmental factors we do not know.

It sounds like your suggesting that a physical change (i.e. Gastric bypass) can cause a genetic change in sperm. Am I understanding your research properly?

BiggerthanSuperman

Ida Donkin: Hi, thanks a lot for your question. No, the gastric bypass does not change the genes of the sperm, it changes the epigenetic patterns of the sperm cells. Epigenetic factors are able to control the expression of the genes, without altering the genetic code (= the DNA) itself.

If you are born with a predisposition for obesity, does this haunt you for the rest of your life?

Will you constantly be required to work out more and eat less than other people in order to keep normal body proportions?

Is it possible for someone with predisposition for obesity to become say, a body builder through a lot of hard work and determination?

ASK_ME_ABOUT_MAGIUM

Romain Barrès: Thank you for your question. To answer your first question, although I don't have experimental evidence to answer, I can speculate that the predisposition in the child should not be fixed, as the predisposition makeup in the dad's sperm itself can be set in a very dynamic fashion (what we showed). In other words, the epigenetic makeup is probably dynamic in fathers AND children, to ensure the dynamicity of the overall phenomenon. Second and third question: Related to my first answer, I think the system should also ensure to be dynamic in the offspring and therefore, no need for continuously erase the "epigenetic programming".