

Peter visscher
[MALE RESPONDENT]
[Other comments:]

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I'd like to start by thanking you for giving me the opportunity to talk about some of our research with the UK Biobank data. Eric Lander put it much more eloquently than I can, but the UK Biobank is really a disruptive data resource, and disruptive here in very positive sense. As you've heard already from many speakers it's not just disruptive in size, it's the data quality, it's the breadth of phenotyping and the model of research and I think it's particularly true for genetics research. If we think about complex traits, and that's what I'm interested in, including common diseases, we've already heard from a number of speakers that UK Biobank has led to the discovery of many genes and gene variants, it's led to, it hasn't been really mentioned yet but it's led to the putative causal epidemiological risk factors for diseases. It's led to the, for the first time for many, many traits, for the estimation of how much genetic variation there is in a population and how traits are correlated with each other. We heard a bit from [?Seth 0:01:14.5] about that, it's actually led to an improved prediction of common disease. What I just want to share with you today is it also allows us to address some very old questions in particular in genetics with new data.

A particular example I want to talk about is assortative mating, which is a form of random, non-random mating with respect to or associated with the spousal similarity, exemplified here as an attraction to do with, on height in this cartoon, as you can see. Why may partners be or look alike? There are a number of possible explanations for that, one is just a social stratification in the population, that you tend to meet your spouse in the same culture or a social setting. One of them, spouses may be alike because of conversions over time, after you've been together for a long time, for example, by having a shared diet, lots of kind of marital interaction. The one I'm particularly interested in is that spouses are alike because they were attractive to each other in the first place because of their phenotypic similarity. There's actually nothing new in observing that spouses are similar to each other, this is a paper from 1903 from [?Pearson and Lee 0:02:40.9] who were interested in quantifying the correlation between first degree relatives for human height, and the data from this actually goes back to the late 1800s.

They also in this paper quantified and I've highlighted this, the spousal correlation for human height, point two eight, and in fact this hasn't changed that much, this is a similar value we have today. It's not just for non-medical traits or model traits like human height that we can observe spousal similarity, here's just an example for psychiatric disorders. Looking at the [unclear word 0:03:22.4] ratio of the spouses of prevalence for a range of psychiatric disorders, and you can see there's a clear elevation there in increased risk, these are just observations in the population. Why do we care, why is it interesting or important to study assortative mating? Actually it has an influence on the population and on genetic variation, so compared to a randomly mating population, if there's like with like assortative mating we get a positive correlation in the genetic predisposition to traits and potentially to disorders. We get an increase of genetic variation and inheritability in the population at large, we get an increase in homozygosity at [?loci 0:04:11.2] that are associated with a trait and which assortative mating takes place, and we get an increase in the correlation between relatives on, in

a reoccurrence risk for disease.

Of course this applies not just to model traits like human height but it also can apply to disease and their risk factors. Just to show you that some of these effects are nontrivial, this is just from pure theory where I show you the relationship between how much the correlation between relatives is increased relative to a random mating population as a function of relatedness of individuals. Relatedness I've got on the X axis here, on the very right hand side is relatedness of one, which is just one monozygotic twin pairs and then a half is parents and offspring, for example, all the way to the left where pairs of relatives only share point one per cent of their genes by, in common by decent. In the red bars here are representing a trait like human height, with a high heritability but a modest spouse correlation, and the blue bars are trait like educational attainment with a lower heritability, with a higher spouse correlation. As you can see on the right hand side this is the ratio of that correlation under the two scenarios, assortative mating, random mating. For distant relatives, so over here for example we get an increase of two to four fold in their correlation, so this has a real effect in the population.

Let's then go to what we did with the UK Biobank data, we approached the question of assortative mating and consequences in two ways. First of all we ascertain spouse pairs through our, about, in the full release about 20,000 or so, and we looked at the association between the phenotype of one spouse and the genotype of their partner, this is one experimental design. In the second experimental design we looked at we just took the genetic data from the UK power bank as if it is a sample of 500,000 genomes from the population. And we looked at the correlation of trait increasing alleles at different [?loci 0:06:31.2] genome, because assortative mating predicts that there will be such a correlation. This is our first example and this was done with the first phase of the UK Biobank release data, so we, to get enough sample size we included data from other sources, which included 23andMe and some other cohorts. What I simply show here is the phenotypic correlation for human height as a trade that's here with the meta-analysis here. Then we said, okay, if there is really assortative mating based upon the phenotypic similarity on height, we should get the same estimate if we look at the phenotype of one spouse and the genotype of the, and the genetic prediction on the trait of their partner.

That's shown over here over at [unclear word 0:07:19.1] the male, there's a focus in the phenotype and then looking at the predicted genetic value or polygenetic value of their spouse or the other way around, and this is the average, when we do it both ways. You can see this value here is exactly, almost exactly the same as the phenotypic correlations, suggesting that this data's completely consistent with the actual, [?made sure it's 0:07:43.3] based partly upon height. We then went to the second study, which is unpublished as yet, you can see it's on bioRxiv like many papers involving UK Biobank data. We wanted here to look at an imprint of assortative mating in the human genome, we did not use any phenotypic information from the UK Biobank in this particular application, what we did is we used [unclear word 0:08:14.9] resource essentially and making predictions from data outside the UK, then predict that in the UK Biobank and looked at a correlation of the trait increasing alleles at the odd numbered chromosomes versus the even number chromosomes,

because assortative mating predicts that there will be a correlation between the two. We did that for a whole bunch of traits, I'll show you here results for two traits where we expected to see an imprint of assortative mating, human height and educational attainment and an [unclear word 0:08:46.6] for which we did not expect to see any.

We did this by the way in three datasets, UK Biobank by far the largest, an American dataset called GERA and another smaller American dataset called HRS. Here are the results for height, so here are the correlation between the trait increasing alleles on odd and even chromosomes in the population, and it's about three per cent or so for human height. It's exactly the same as what we predicted from theory without actually doing the analysis. Similarly an observation on educational attainment where it would also be observed imprint of assortative mating is the same as what we predicted. For our [unclear word 0:09:28.8] bone mineral density we don't see anything. Then we took the same traits plus another 30 traits that included diseases and disorders and we went back now to the full UK Biobank dataset of 20,000, spouse pairs of 20,000 - sorry. The full UK Biobank set where there was 20,000 spouse pairs and we compared here on the X axis our estimate of this correlation, this imprint of assortative mating in the genome, in the UK Biobank genome and we compare that to the correlation of the predicted value in the spouses for all of those traits.

Here most of the traits don't show any results and we think this is partly because we still lack power, not in terms of the dataset of the UK Biobank, but in the prediction accuracy of a number of traits and disorders, for example, liability to schizophrenia I think is this one over here, so maybe with future datasets we will see an effect there. The only effects that clearly show up are height and educational attainment and again, they are completely in line with what we predicted beforehand. I'd like to thank, sorry, I'd like to end also by thanking the people that made this happen, the UK Biobank. It's an amazing, an amazing resource to work with and from what we've heard today there's a lot more to come. I'd like to point out, well first of all thank you to Naomi for showing Australia on the map, our whole group, the majority of these people actually working on UK Biobank data, on a whole, whole range of different projects including Type 2 diabetes and many, many other questions. I'd like to thank Loic and Matt who did the most work on the assortative mating project and Matt's now at the University of Lausanne. Thank you for your attention.

[END OF TRANSCRIPT]