General Session IV: Predictors of Exceptional Longevity Q&A

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Question From the Floor: In the genetic studies of siblings, my first question is: do you confirm common maternity and paternity or do you take their belief at it? And second, have you seen similar findings in half-siblings? I guess what I'm really getting at is, are you sure all 12 children are from the same mother and father?

Tom Perls: We have not yet done and maybe I'm not the right person to answer this question, but at least in our studies we have a substantial number of offspring, but we are still yet to tackle looking at the genetics and the genetic signatures of those kids, but absolutely we would do a careful job of doing what's called a forensic profile to make sure of the relatedness of the individuals.

Jay Olshansky: I have two questions for Tom. The first one is on personalized genomics. As you know there's this wonderful anti-aging industry that is already selling personalized genomic kits designed to tell you what kinds of diseases you're susceptible to and then they're perfectly willing to sell you products designed to treat those diseases so here's a soft ball question: What do you think about these personalized genomic tests?

And then the second question actually has to do with one of the first comments that you made, which was that all of us could expect to live to about 88. Did I read that correctly?

Tom Perls: I thought quite a bit more than that. I mean the average Seventh Day Adventist, the average life expectancy for Seventh Day Adventist is 88 years so I think a lot more people should be able to get to that age with good health habits, I think.

Jay Olshansky: Maybe I misheard because what I thought I heard you say was we could all expect to live to about 88 which would mean, of course, our life expectancy would be much greater than that, so what I thought you meant to say was about half of you could expect to live

to about 88 and the other half would die before that so I wasn't quite sure about the way in which you meant to say that.

Tom Perls: Thanks for preaching to the choir regarding the anti-aging industry and personal genomics. I already had mentioned that I didn't think that personal genomics was ready for prime time. The FDA and Congress have actually also voiced concern and caution over this and it isn't just the anti-aging industry, but we see these kits now in pharmacies and so on. If I heard that I was homozygous for apolipoprotein E4 and I wasn't already really interested in my health habits that might push me in the direction of wanting to do more in terms of looking at my other cardiovascular disease risk factors and what have you because that would be pretty alarming to me. But beyond that I think and we actually have a very few number of centenarians who have APOE4 and that speaks to the issue that they have something else that's countering that. But beyond that the suite of other variance that these companies are proposing can help them predict with $400 of your money so you would think that would be a pretty high prediction, that they can you help you out. I think it's not at all ready because of the fact that we need to have a better handle of what other genes and lifestyle habits could be affecting your risk.

Jean-Marie Robine: I have two questions, one for Tom, one for Valerie. The first one is, how many SNPs did you check into, can you remind me? And for Valerie, I think you used the 1895 cohort as a control. Can you just tell us why you chose exactly this cohort?

Tom Perls: My answer is very quick. You start off with a chip that has about 350,000 markers on it and after you do some cleaning and what have you, I think we ended up with about 295,000 markers. Now, we have chips with two million markers.

Valerie Jarry: Siblings of centenarians were born on average in 1895. It was thus appropriate to use the 1895 birth cohort as a control group because it was the same cohort as our master sample. It was simply the best match. Thank you.

Paul Sweeting: I had a couple of questions. First was for Leonid. In relation to life expectancy and month of birth, I was wondering if you had looked at or if anybody has looked at infant mortality and stillbirths around 100 years ago by month as well, see what effect that might have had, whether it was just a selection effect, that it's only the strong babies that survive and then go rather than anything about the conditions in utero.

And the second question, which is especially for Valerie and Tom, looking at the relationship between the gender of siblings and centenarians and the way in which those interact, I wondered what that told us if anything about the importance of genetic markers on the X and Y chromosomes for longevity and also if there's any investigations into fathers and mothers and sons and daughters to again see the importance of genetic markers on the X and Y chromosomes on longevity.

Leonid Gavrilov: Thank you for your question. We are acutely aware that there is a seasonality of infant mortality and for this reason you cannot analyze just life expectancy at birth, simply because seasonality in child mortality could be a trivial explanation for observed month-of-birth differences in human lifespan. For this reason, in our first genealogical study we made data cut-off at 50 years of age. Our study subjects and their siblings had to survive to 50 years, and then we analyzed what are the chances to live to 100 years for those individuals who survived to 50 years of age. In this case, of course, all deaths before age 50 were eliminated, thus eliminating direct effects of seasonality in infant mortality on life expectancy. Of course, there may be indirect effects of seasonality of infant mortality and stillbirths through the selection mechanism and this hypothesis could be tested in further studies. In our second study of seasonality we used the Social Security Death Index and we analyzed single-year birth cohorts and calculated life expectancy at the age of eighty years. We found that eighty years later it still matters in which month you were born! Here again infant mortality rate has no direct impact on lifespan, because the remaining life expectancy at age 80 was studied.

Also I would like to add that it is very important to study month-of-birth effects in real birth cohorts, controlling for the exposure data. This is important because a similar study by Doblhammer was mentioned at this meeting without recognizing its flaws. That study used a cross-sectional set of death certificates without proper control for the number of people exposed to the risk of death. It's like you go to the cemetery and write down at which months some persons were born and then calculate their life span. This cross-sectional approach of mixing together different birth cohorts is flawed and produces misleading and pretty wild results. For example, those people who were born many, many years ago have very poor education levels, because in history there was an improvement in education attainment. And then because they died at old ages one can make an erroneous conclusion that it is good for longevity to have low education level. That's exactly what was found in the study by Doblhammer. In general, if there is any change in the seasonality of births over historical time, so that the older birth cohorts have different seasonality of births, then the cross-sectional approach leads to an erroneous conclusion of seasonal effects on longevity, even if they do not really exist. So there is a fundamental difference between our studies and the study of Doblhammer that we made analyses in the correct way by studying real extinct birth cohorts.

There was also a question on the quality of our data on centenarians. In brief, the data quality is high because information about centenarians was taken not from the recent census claims, but from the Social Security Death Index matched with genealogical records. In our study we used only early censuses to validate the date of birth of future centenarians, when they were young children.

Tom Perls: The issue of the X and Y chromosome is really interesting and Valerie's finding that it mattered if your centenarian sibling was a male and maybe not so much as a female, and the fact that men just have one X chromosome as opposed to women with two, maybe playing a role there in terms of either the homogeneity or the significance of what the men are portraying there versus the greater heterogeneity with the two X chromosomes among the women and there is a huge number of really important DNA repair and other genes that

actually, as Len had mentioned, would be important to cell maintenance on the X chromosome. That's of really incredible interest to us. And maybe playing an interesting role in this as to why women live longer than men and that's a whole different topic. But genome-wide association studies don't do a good job of looking at the X chromosome, and so until we start doing big sequencing studies where you can look at the X chromosome we're not going to see those findings come out. And now that we really are going away from GWAS and going to whole genome sequencing, I think we're going to see a huge amount of interesting information come out about X chromosome. Thank you.

Hiram Beltran-Sanchez: My question is for Gavrilov. In your conclusion of your results you mention that probably the reason why the first member of the family made it to 100 was because of the oocytes being early. So my question is whether you have considered allocation of resources within the family meaning nutrition as an alternative explanation. There is some work by economic historians, particularly Fogel, who have shown that within a family when they use height as an approximate measure for maturation in childhood, the first member of the family is taller than their siblings. This suggests the first family member usually gets more nutrition, so along these lines we would expect a stronger effect in smaller families as opposed to large families, which is exactly what you found. In a smaller family there is a stronger effect in the first sibling as opposed to large families who will have fewer resources. So my question is whether you have considered nutrition.

Leonid Gavrilov: Yes, it makes perfect sense. In fact when we first demonstrated the effect of the birth order, we presented this as a hypothesis not as an explanation so, of course, the more hypotheses you have the better. And in our first study we initially found the effect of the birth order. Yet, when we analyzed more data, we eventually found that birth order is not a statistically significant predictor of longevity, when the maternal age variable is also added into analysis. It happened so that we initially didn't have a sample of sufficient size to study effects of the age of parents on longevity.

Natalia Gavrilova: Initially we made some preliminary study on a smaller sample completely different and have found the effect of birth order. But, in this larger sample, we did not find any effect of birth order, and we put it into equation but birth order was not a statistically significant predictor of survival to age 100, while age of mother was, so we believe that this probably is not this allocation of resources to the first child, which is responsible for longevity and there is probably something related to the age of mother.

Leonid Gavrilov: And also if you look for the scientific literature you can find that the offspring of younger mice live longer lives, and in laboratory mice the allocation of resources between offspring is not an issue. So it's a really more general biological explanation of maternal-age effects that might be considered. But, you're quite right that the hypothesis of resources allocation is a viable hypothesis in humans, and we can continue to collect different data sets and to work with this hypothesis. Simply because the same phenomenon is observed also in laboratory mice, we are more prone to biological explanations based on the higher quality of younger oocytes.

Sam Gutterman: Over the last several decades we have seen a delay in average ages of birth mothers. Do you believe this trend could have a negative impact on future mortality?

Leonid Gavrilov: Yes, this is quite true and in American society women are strongly motivated to build their career and therefore they postpone the births. There is some cost involved in delayed motherhood and there is an abundance of medical literature demonstrating this. The risk for Down's syndrome, for example, is increasing exponentially with a mother's age, but this is part of the story for early life events and early outcomes. Here we studied the opposite part of the life cycle, an exceptional longevity, and we found that even late in life it still matters what was the age of your mother. For example, we looked at differential survival after age 70, and if you compare siblings at age 70, some of them live to 100 and some don't. Even at age 70 it still matters what was the age of your mother in terms of predicting survival to 100 years. So it's a late-life effect and the same is observed in laboratory mice. In the first half of the

mouse life the survival is the same regardless of maternal age, but later in life you can see profound difference in survival of offspring depending on the age of the mother.