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The Genetics of Methuselah

Focus On Future Medicine

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Research into genes related to aging is just beginning. You are listening to reachmd.com on XM160, The Channel For Medical Professionals. Today, we have a special segment on the Future Of Medicine. Welcome. I am your host, Dr. Maurice Pickard, and joining me today as our guest is Dr. Nir Barzilai. Dr. Barzilai is the Director of the Institute for Aging Research at Albert Einstein College of Medicine and is also professor of Medicine and professor of Genetics at the same institution.

DR. MAURICE PICKARD:

Thank you very much for joining us today.

NIR J. BARZILAI, MD:

Please to be with you.

DR. MAURICE PICKARD:

With 55,000 centenarians existing now and some people say that by the year 2050, it will be 800,000 centenarians in the United States. In other words, this is the more rapidly growing cohort that we had. Is it time that we begin to include them in our medical research?

NIR J. BARZILAI, MD:

Absolutely time because we have learnt a lot from centenarians. Basically, we have learnt what's their phenotype and what's part of their genotype that allowed them to get to this age with few age-related diseases.

DR. MAURICE PICKARD:

Well, what is the lipoprotein phenotype that you found in this particular segment of our population?

NIR J. BARZILAI, MD:

The families of centenarians have an increased levels of HDL cholesterol and very large lipoprotein particle size, that is, the size of the HDL and LDL molecules. If your HDL is high and you have a father who is a centenarian, this would be a good prediction for long life according to our study.

DR. MAURICE PICKARD:

Well, who did you use in your study and why did you select them?

NIR J. BARZILAI, MD:

Because we are focussed on genetic discoveries, it's always important to study a population that is relatively homogeneous from a genetic point of view. The Amish in Pennsylvania, the Icelandic and Ashkenazi Jewish are very good examples of people that came from relatively few founders and there are many of them now so that you can remake a genetic relation to some of the diseases that they have.

DR. MAURICE PICKARD:

Who controls them?

NIR J. BARZILAI, MD:

Because people who are born together with centenarians have died 40 or 50 years ago. We obviously have a problem to put the correct control and what we have been doing we have been recruiting the offspring of centenarians that we think have inherited their longevity genes or half of them have inherited the longevity genes and we matched them with age match and gender, controlled their age, which is approximately 70 years old. And so, the genetic studies are between those unrelated people, the age match control, and the centenarians, but our validation are actually in the offspring of centenarians that they have a much larger percentage of genotype for longevity.

DR. MAURICE PICKARD:

Well, will it control also Ashkenazi Jews even though they were not related to the probing?

NIR J. BARZILAI, MD:

Yes, the whole population is of Ashkenazi Jews.

DR. MAURICE PICKARD:

Well, do they have the lipoprotein phenotype that you saw in the offspring?

NIR J. BARZILAI, MD:

No, they had a much worse phenotype. They had the normal expected HDL levels, which are 45 for men and 55 for women and they didn't have with the population the large lipoprotein particle size.

DR. MAURICE PICKARD:

Was there any associated genotype to go along with this?

NIR J. BARZILAI, MD:

Yes, there were several genotypes for lipoprotein and in fact they were three that were validated and the interesting thing with all those genotypes is that their homozygosity percentage at 60 years old was about 8 to 10%, but it was although represented in centenarians, so it was between 24 and 32%. So, they really accounted for a major increase in our centenarians and since each one of them had a functional role, we think that it really was very much associated with their longevity and was associated with prevention of not to one, but several age-related diseases.

DR. MAURICE PICKARD:

Is there a name for their genotype?

NIR J. BARZILAI, MD:

One of the genes, the first one that we established is called CETP or cholesteryl ester transfer protein gene and that's a pass way that is involved in both increasing HDL cholesterol and lipoprotein particle size and also in the transfer of cholesterol from lets say our coronaries to the liver and out of the body.

DR. MAURICE PICKARD:

Is there a possibility that some day there may be medications that would affect the gene?

NIR J. BARZILAI, MD:

Actually there is in particularly to this genotype. Our other genotypes haven't been re-probed yet by the pharmaceutical, but for reasons that are not related to longevity because of their effect of lipoprotein, there are several drug companies that are doing inhibition to CETP, which is what the genotype is doing in order to treat hyperlipidemia and if we predict correctly, it will be used not only for prevention of hyperlipidemia, but to prevent several age-related diseases and that's is very exciting.

DR. MAURICE PICKARD:

If your just joining us, you are listening to reach.com on XM-160, The Channel For Medical Professionals, and today we have a special segment on the Future Of Medicine. And we are discussing the interesting results of new genes that are found in the elderly part of our population that may have significance to all of us. I am Dr. Maurice Pickard, your host, and with me is Dr. Nir J. Barzilai who is the Director of the Institute for Aging Research at the Albert Einstein College of Medicine.

You began to tell me that there is the hope that there will be drugs that will affect these genes and that it may not only affect the cholesterol or lipoprotein, but is it possible that it would effect say cardiovascular disease, hypertension, or most obvious thing would be to say the metabolic syndrome that we all talk about.

NIR J. BARZILAI, MD:

There are certain association between prevention of all those diseases in people who have this genotype and the low level of CETP and also the good lipoprotein profile. I think the most exciting example is the fact that when we looked at the cognitive function of our centenarians and we did a Mini-Mental state exam that has 30 questions and we decided if you pass 25, you did very well. We tried to identify how come some 100 years old get with their brain and not only with their body to age 100 and we found that those people were the ones who had 3 times more of the CETP good genotype than the ones who didn't do well in the state exam and we repeated the same study in the Ashkenazi Jews at the Einstein Aging study and we showed that people who had dementia, their CETP genotype was five times less prevalent than people who didn't become demented. In other words, there is a direct association between the CETP genotype and cognitive function and I think that this is very promising for not only the diseases that you said, but also for prevention of Alzheimer and cognitive decline with aging.

DR. MAURICE PICKARD:

Is CETP found actually in the brain as APOE, which is the one that we associate with Alzheimer's found in the brain.

NIR J. BARZILAI, MD:

Yes it is expressing the blood brain barrier of humans and our data indicate that it's even more expressed, which is bad in Alzheimer patients. So, the idea that there is something directly in the brain is something that we are actually looking at.

DR. MAURICE PICKARD:

And I certainly grew up with George Burns, Strom Thurmond, and recently Anne Nixon Cooper, the 106-year-old who President-Elect Obama mentioned in his speech on election night has it been on the air, we have a lot of people to look at and I wonder, although you used this particular group, are there going to be other opportunities to study other centenarians?

NIR J. BARZILAI, MD:

The first point I want to make is that, for me it was just interesting that President-Elect Obama didn't talk about diabetic patient or cancer patient. He chose of everything to talk about a 106-year-old woman and I hope that's predictive for the funding that we will get into this research. The other point I want to make is that it's important to study the centenarians now because what you said is the growth of centenarians from 55,000 to may be million, in fact, there are some people who are saying that every child that will be born now would live to age 100, but this will be true mainly by technology. They are not going to be the pure people who get there. They are going to be the bionic people who get there with bypasses, with pacemakers, with artificial limbs or after operation and I think it's important to take the people who are naturally going there and studying them because otherwise this will be a missed opportunity.

DR. MAURICE PICKARD:

The other thing that you've written about and I would like to just touch on it is the functional significance of insulin growth factor in the elderly and I wonder if you take us into that and especially the receptor site.

NIR J. BARZILAI, MD:

Yes, you know it's really very interesting in nature. You know the pony lives longer than the horse and the small dogs live longer than the large dogs and if you take mice and either mutate their growth pathway or if they are happen to be born with a form of dwarfism, they all live longer. And so, the idea that this growth is involved in aging is something that many investigators are looking at. And because of that, we actually were sequencing the IGF receptor, which is where most of growth hormone action is going to occur. A growth hormone will increase IGF and IGF will bind to its receptor and we will start doing all that it has to do to promote growth and well being of cells. Well, we sequence those IGF receptors and we found seven women centenarians whose IGF receptor had a mutation that led to inactivity, which we looked at also. It's not that the majority of our centenarians are kind of a dwarf or have impaired growth, but it is probably one pathway that allow centenarian to reach this age.

DR. MAURICE PICKARD:

You know, as a sportsman the hit home runs, you got to take growth factor. There seems to be a conflict or is there a short-term effect it is and a long-term effect?

NIR J. BARZILAI, MD:

Well, that's I think exactly the point growth factors and estrogen, for example, sex hormones are definitely useful hormones and they work great on both these of young people. The question is what happens when you do a very unidimensional study and you give either estrogen or growth hormone in isolation to somebody who is 60 or 70 years old and has an old body. Can the old body with its environment of aging with more Cenestin cells and other things that happening in the body can build all body tolerate well those youthful hormones. Now, from the estrogen study on the women health initiative, we know that when you give it to 60 years old, they develop cognitive dysfunction, heart disease, and breast cancer. So, obviously it's not so good for prevention of age-related diseases. I think our study on the IGF receptor suggest that actually the people that live longer are those that have low-growth hormone levels or action and not the others. So, I think yes exactly your point is right. You should be cautious when you give to elderly person growth hormone because I would predict it would do the opposite and will not be safe.

DR. MAURICE PICKARD:

That's interesting. You say that reduce growth factor or growth hormone factor I leads to a longer life. Well, doesn't calorie restrictions do the same thing, reduce growth factor I and does that also lead to increased age. In other words, is just a plug that we better watch our calories and this is in some way related to this pathway that you are working with.

NIR J. BARZILAI, MD:

Yes, you are absolutely right. Look caloric restriction is really the best-known model to increase lifespan in variety of animals. I just have to tell you with caution that it has not been shown to be as effective in primates and it certainly hasn't been effective in humans, although one thing we know is that obese people live shorter life than lean people. It might be a relevant paradigm or not, but caloric restriction is the way to retard age in animal models and one of the things that happen in caloric restriction is that there is less IGF levels. Is this the reason for the longevity, I am not sure. I should also say that the caloric restricted studies in humans, IGF does not decrease, but many of the other features of caloric restriction are established. So, we don't know the answer, but certainly the growth hormone factors and certainly the caloric restriction are part of the most exciting paradigm in aging that we are trying to translate into human research and understanding health span.

DR. MAURICE PICKARD:

Well, this talk has certainly been an exciting one. Certainly, the future of gene research is there for all of us and hopefully we will all benefit from it and I think we have to remember that we have to also do something as simple as watching our calories and I want to thank Dr. Nir Barzilai for being with us. He is the director of the Institute for Aging at Albert Einstein College of Medicine and I am your host, Dr. Maurine Pickard, and you have been listening to a special segment on the Future Of Medicine from reachmd.com on XM 160, The Channel For Medical Professionals. Please visit our website at reachmd.com which features an entire library through on-demands podcasts or call us toll free with your comments and suggestions at 888-639-6157. Thank you for listening.

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