The New England Centenarian Study Newsletter

Geriatrics Section, Department of Medicine
Boston Medical Center, Boston, MA, USA

January 2012 Volume 9.1

Happy New Year!

It is our pleasure at the New England Centenarian Study to wish our study participants and their families a wonderful New Year for 2012!

Thank you Marty and Paulette! We send out a very special thank you to Marty Samowitz and his wife Paulette, who recently provided the Study with a very generous donation which in part allows us to send this newsletter out to all of you.

We want to bring you up to date with what we have been up to lately and our recent exciting accomplishments. We continue to enroll new participants in our various studies as well as conduct our annual collection of data on all of our previously enrolled subjects. These yearly follow-ups allow us to assess changes in health and function over time. As you will see many of our findings are a result of these follow-up data, so we extend our sincerest gratitude for all of your help and continued participation.

This month has been a flurry of activity for us as we had three different papers published and as a result, quite a bit if media attention.

We published in January of this year the corrected version of our paper that originally came out in *Science* last year: **Genetic Signatures of Exceptional Longevity in Humans.** The major scientific findings were generally the same, but there were substantial technical differences that merited publication of the corrected version in another journal. The major (but many) findings of our research were:

- Genes play a critical and complex role in facilitating exceptional longevity
- Because many genes are involved, one needs to include many different genes at once (rather than rely on single genes, one at a time) to predict who is a centenarian, using genetic data alone.
- We found 281 genetic markers that are 61% accurate in predicting who is 100 years old, 73% accurate in predicting who is 102 years old or older and 85% accurate in predicting who is 105 years old or older. In other words the prediction gets better with older and older ages beyond 100 which goes along with our hypothesis that the genetic component of exceptional longevity gets greater and greater with older and older age.
- These markers point to at least 130 genes, many of which have been shown to play roles in Alzheimer's, diabetes, heart disease, cancers, high blood pressure, and basic biological mechanisms of aging.
- Centenarians have just as many genetic variants that are associated with increased risk for age-related diseases (like Alzheimer's, heart disease, stroke, diabetes and cancer) as people in the general population. Therefore, their tremendous survival advantage may in great part be due to the existence of longevity associated genetic variants.
- People have genetic profiles that can be constructed from these 281 genetic markers (each of which has 3 variations) and these in turn are associated with specific probabilities of achieving very old age. Very interestingly, subjects in both the

control groups and the centenarian group have profiles in common that we call genetic signatures. Ninety percent of the 801 centenarians in the New England Centenarian Study could be grouped into one of 27 genetic signatures.

- These genetic signatures are also associated with different predispositions to subgroups of centenarians such as those that completely escape heart disease, or those that delay Alzheimer's disease until the last 5% of their very long lives. We believe that method for producing these signatures will be very useful for better understanding the underlying genetics of protection from age-related diseases and for the field of personal genomics.

Citation: Sebastiani P, Solovieff N, Puca A, Hartley SW, Melista E, Andersen S, Dworkis DA, Wilk JB, Myers RH, Steinberg MH, Montano M, Baldwin CT, Perls TT. Genetic Signatures of Exceptional Longevity in Humans. *PloS ONE* 2012. DOI: 10.1371/journal.pone.0029848. URL: http://www.plosone.org/article/info:doi/10.1371/journal.pone.0029848

In another paper published this January, we have produced perhaps some of our most exciting findings to date. Early in our studies (The New England Centenarian Study began in 1995), we thought that centenarians had to markedly delay or even escape age-related diseases like heart attacks, stroke, diabetes and Alzheimer's, or else they would never be able to get to their very old ages. In fact, in 1980, a Stanford researcher named James Fries proposed the "Compression of Morbidity" hypothesis which states that as one approaches the limit of human life span, they must compress the time that they develop diseases towards the very end of their life and he proposed that people around the age of 100 do this. However, in 2003 we found that many of our centenarian subjects had age related diseases even before the age of 80 (about 43%, and whom we called "survivors"), after the age of 80 (about 42%, and whom we called "delayers") and lastly, those who had no mortality-associated diseases at age 100 (about 15%, and whom we called "escapers").

Sarah Knauss, our oldest subject ever at the age of 119 yrs

The key though was that 90% of all of the centenarians were still independently functioning at the average age of 93 years. Somehow, despite the presence of diseases, people who become centenarians don't die from those diseases, but rather they are able to deal with them much better than other people and remain independently functioning more than 30 years beyond the age of 60.

In this current paper though, titled **Health span approximates life span among many supercentenarians: Compression of morbidity at the approximate limit of life span**, we have found that we just weren't looking at old enough subjects when investigating Jim Fries' hypothesis. After all, the oldest person ever was 122 years old (she died in 1997) and people who live to 110+ years occur in the population at the rate of about one per 5 million, while people who live to 100 are much more common at the rate of one per 5,000. So, surviving to age 100 is very special relative to the general population and surviving to 110+ years is very special relative to people who live to around 100.

As some of you know, over the past few years we have been working hard on recruiting and enrolling the most extreme old, supercentenarians who are people that live to 110 years and older. Once we enrolled our hundredth supercentenarian (by far the largest collection of supers in the world), we were able to investigate whether or not people who truly approach the limit of human lifespan actually compress their morbidity towards the end of their lives.

In comparing controls, nonagenarians (subjects in their nineties), centenarians (ages 100-104), semi-supercentenarians (ages 105-

109) and supercentenarians (ages 110+), the subjects had progressively shorter periods of their lives spent with age-related diseases, from 17.9% of their lives in the controls, to 9.4% in the nonagenarians, down to 5.2% in the supercentenarians. These findings support the compression of morbidity hypothesis and the idea that there truly is a limit to human life span and that this limit is around 110-125 years. Also, the supercentenarians were much more alike in terms of the markedly delayed age of onset of age-related diseases compared to the subjects age 100-104. That homogeneity indicates they must have some factors (presumably genetic) in common that allow them to be so similar.

Citation: Andersen SL, Sebastiani P, Dworkis DA, Feldman L, Perls T. Health span approximates life span among many supercentenarians: Compression of morbidity at the approximate limit of life span J Gerontol A Biol Sci Med Sci 2012;doi:10.1093/gerona/glr223.
URL:
http://biomedgerontology.oxfordjournals.org/cgi/reprint/glr223?ijkey=dClzzexYazWo3cQ&keytype=ref

frontiers IN GENETICS OF AGING

In our third paper published this January, the New England Centenarian Study, along with collaborators at the Scripps Institute and the University of Florida, Gainesville, performed and published the first-ever whole genome sequencing of a supercentenarian – and actually not one super, but two, both over the age of 114 years and one was a man and the other a woman. As with our paper on the genetic signatures of exceptional longevity, we found here as well that centenarians have just as many genetic variants associated with diseases as the general population. However, they likely also have longevity-associated variants that counteract such disease genes thus allowing for slower aging and increased resistance to age-related diseases. In this paper we also found several genes that occurred in our published genetic prediction model which had coding regions that led to differences in gene function. These findings support the validity of the genetic prediction model. The New England Centenarian Study has posted the whole genome sequences of these two subjects on a data repository (called dbGaP) based at the National Institutes of Health. This will allow researchers from around the world to access all of the data and use them for their own research. Our hope is that these data will lead to important discoveries about genes that help delay or allow the escape from age-related diseases like Alzheimer's disease.

Citation: Sebastiani P, Riva A, Montano M, Pham P, Torkamani A, Scherba E, Benson G, Milton JN, Baldwin CT, Andersen S, Schork NJ, Steinberg MH, Perls T. Whole genome sequences of a male and female super-centenarian, ages greater than 114 years. Frontiers in Genetics of Aging 2012;2. URL: http://www.frontiersin.org/genetics_of_aging/10.3389/fgene.2011.00090/abstract

The New England Centenarian Study

Please visit our website at www.bumc.bu.edu/centenarian for additional information and, as always, if you have any specific questions that we might be able to answer for you, please call or email us (our email addresses and phone numbers are listed at the end of the newsletter).

Staff Comings and Goings:

We wished a fond farewell to Alex Nordberg as she went off to medical school (New York Medical College) last summer, as well as to Nick Solovieff who is concentrating full-time on his Physician's Assistant schooling. Jaimie Huntly left to embark on some international travel as she awaits her acceptance letters to medical school.

We are so pleased to recently welcome Dr. **Barbara Kager PhD** who has her doctorate degree in Gerontology and who is recruiting and enrolling subjects and collecting data for our Archon Genomics X Prize Study.

In 2011, we welcomed on board **Jesse Gass, MPH**, who comes to us from Columbia University. Jesse is intensely interested in clinical psychology and as she gains experience here at the NECS, we anticipate that Jesse will be applying for doctoral programs in clinical Psych. **Tara Neary, BA**, is our first ever graduate of a college degree program (Holy Cross) in Gerontology! We are so pleased to have Tara while she gains clinical research experience before going to medical school (knock on wood!).

In addition to directing the NECS and the LLFS as well as helping with the recruitment of centenarians for the Archon Genomics X Prize, and his clinical duties as a staff geriatrician at Boston Medical Center, **Dr. Perls** has been working hard on applying for federal and foundation grants to support our research activities.

Stacy Andersen, Project Manager, is in the throes of data collection for her dissertation for her Ph.D. in Behavioral Neuroscience at Boston University, and **Lori Feldman** is enrolled in the Master of Social Work program at Salem State University.

Tom Perls MD, Tara Neary, Jesse Gass, Stacy Andersen, Barbara Kager and Lori Feldman

The Long Life Family Study

The Long Life Family Study (LLFS), a multi-center study of familial longevity, funded by the National Institute on Aging, is in its 7th year. The LLFS studies 550 families that have remarkable clustering for exceptional longevity. There are a total of 4,400 family members in the study! We are continuing to follow up with all of the participants over the phone and we could not have asked for a more wonderful and interesting group of subjects to work with! The LLFS is currently in the midst of finishing up the generation of a tremendous amount of genetic data from our subjects' DNA samples and very soon we will be embarking on the data analysis and hopefully some very interesting and helpful discoveries are around the corner! Our LLFS subjects will notice that we have recently added some new questionnaires that address the possible connection between sleep habits and activity level with longevity. We thank you all very much with all of your helpful answers to these questionnaires.

The Cognitive Function in Long-Lived Families Study

Since December, 2010, we have been enrolling Long Life Family Study participants who live within 3 hours of Boston for participation in a 3 hour in-person study of cognition called the Cognitive Function in Long-Lived Families Study. To date, we have enrolled 158 participants from both generations of the Long Life Family Study. In addition, we have enrolled 41 participants from our control group. We are using tests of memory and executive functions (higher-order thinking abilities) to look at how memory and thinking change with age and how being part of a long-lived family may be beneficial. We hope to start an initial round of data analyses over the next few months. We are truly thankful to everyone who has agreed to take part in this additional study and have enjoyed catching up with you since the first in-person assessment!

Centenarian Highlight:

Howard Rees and sister Jane Turley in October, 2011, at her 100th birthday party. Howard is 102.

Gerontological Research Meetings:

The Gerontological Society of America Annual Scientific Meeting was held in November in Boston, MA this year.

- Stacy Andersen BA presented a poster on our findings on Personality Factors in the Long Life Family Study (LLFS). We analyzed factors of personality from a personality questionnaire called the NEO-Five Factor Inventory. This questionnaire evaluates personality characteristics of neuroticism (lack of emotional stability), extraversion (being outgoing), openness to experience, agreeableness, and conscientiousness (dedication). We found that offspring from long-lived families score lower in neuroticism and higher in extraversion and agreeableness compared to the general population. This provides evidence that personality factors may play a role in achieving a long life.
- Tom Perls MD, MPH and Paola Sebastiani PhD presented their work titled Health Span Approximates Life Span Amongst Many Supercentenarians.
- Dr. Perls also participated in a news conference introducing The Archon Genomics X PRIZE: The Genetics of Exceptional Longevity.

Recent Publications:

1. Newman AB, Glynn NW, Taylor CA, Sebastiani P, Perls TT, Mayeux R, Christensen K, Zmuda JM, Barral S, Lee JH, Simonsick EM, Walston JD, Yashin AI, Hadley E. Health and function of participants in the Long Life Family Study: A comparison with other cohorts. *Aging* (Albany NY). 2011 Jan;3(1):63-76.

2. Kulminski AM, Arbeev KG, Christensen K, Mayeux R, Newman AB, Province MA, Hadley EC, Rossi W, Perls TT, Elo IT, Yashin AI. Do gender, disability, and morbidity affect aging rate in the LLFS? Application of indices of cumulative deficits. *Mech Ageing Dev.* 2011 Apr;132(4):195-201. Epub 2011 Apr 2.

3. Solovieff N, Hartley SW, Baldwin CT, Perls TT, Steinberg MH, Sebastiani P. Clustering by genetic ancestry using genome-wide SNP data. *BMC Genet.* 2010 Dec 9;11:108.

4. Sebastiani P, Riva A, Montano M, Pham P, Torkamani A, Scherba E, Benson G, Milton JN, Baldwin CT, Andersen S, Schork NJ, Steinberg MH, Perls TT. Whole genome sequences of a male and female supercentenarian, ages greater than 114 years. *Front Gene.* 2012 2:90.

5. Andersen SL, Sebastiani P, Dworkis DA, Feldman L, Perls TT. Health span approximates life span among many supercentenarians: compression of morbidity at the approximate limit of life span. *J Gerontol A Biol Sci Med Sci.* 2012.

6. Sebastiani P, Solovieff N, DeWan AT, Walsh KM, Puca A, Hartley SW, Melista E, Andersen S, Dworkis DA, Wilk JB, Myers RH, Steinberg MH, Montano M, Baldwin CT, Hoh J, Perls TT. Genetic signatures of exceptional longevity in humans. *PLoS ONE.* 2012 7;1:108.

7. Barral S, Cosentino S, Costa R, Matteini A, Christensen K, Andersen SL, Glynn NW, Newman AB, Mayeux R. Cognitive function in families with exceptional survival. *Neurobiol Aging.* 2012 Mar 33;3:619.

8. Stern RA, Andersen SL, Gavett BE (2011). Executive functioning. In A. E. Budson & N. W. Kowall (Eds.), *The handbook of Alzheimer's Disease and other dementias* (pp 369-415). : West Sussex, UK: Wiley-Blackwell.

Articles are or will be made available online:
http://www.bumc.bu.edu/centenarian

Our contact information at Boston Medical Center:

The New England Centenarian Study
Boston Medical Center
88 East Newton Street, Robinson 2400
Boston, MA 02118

Toll-free number 888-333-6327

Thomas T. Perls, MD, MPH 617-638-6688
Email: thperls@bu.edu
Stacy Andersen, BS 617-638-6679
Email: stacy@bu.edu
Lori Feldman, BA 617-638-6433
Email: lorif@bu.edu
Jesse Gass, MPH 617-638-6432
Email: jdgass@bu.edu
Tara Neary 617-638-6680
Email: tmneary@bu.edu
Barbara Kager
Email: mbkager@bu.edu

Funding and Donations:

Funding of our research primarily comes from peer-reviewed competitive grants provided by the National Institute on Aging (NIA) and the National Heart Lung and Blood Institute (NHLBI), both of the National Institutes of Health (NIH). We are extremely thankful to the Glenn Medical Foundation which provided a grant award to Dr. Perls to study the basic biological mechanisms of aging.

For anyone interested in philanthropic support of the Study or if you know of someone you would like Dr. Perls to contact, please let him know at 617-638-6688 or email him at: thperls@bu.edu. **Any and all donations are needed and so appreciated.**

Recruitment:

We are always looking for participants throughout North America for our studies. If you know of any centenarians age 105 and older who may be interested, please call our study toll-free at **1-888-333-NECS (6327)** or email Stacy Andersen (stacy@bu.edu).

Send us your pictures!

We love getting your pictures! Please send us your photographs. We make regular submissions to various media and we love being able to include photographs of our amazing participants. If we decide to use your photo for any reason, we will contact your family to obtain permission.

If you wish, we will be happy to return any photographs to you.

Websites of Interest:

Our studies:
www.bumc.bu.edu/centenarian
www.bumc.bu.edu/supercentenarian
www.longlifefamilystudy.org

A website about anti-aging quackery and growth hormone
www.hghwatch.com

The Life Expectancy Calculator
www.livingto100.com