The ClinSeq™ Newsletter

Volume 2, Summer 2009

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Dear ClinSeq™ Participant,

Welcome to the second edition of the ClinSeq™ Newsletter! For those of you who are new to the study, or for whom this is your first newsletter, we encourage you to visit the ClinSeq™ web site to check out the original newsletter. We plan on sending newsletters, such as this one, periodically so that you are up-to-date on the study and aware of key findings that may come up in the future. Please note that you can find an electronic version of this newsletter and the first edition on our website at www.genome.gov/clinseq

The study has been going extremely well, with excellent ongoing enrollment and some exciting scientific advances and presentations. A few of these are outlined in this newsletter. I would like to take this opportunity to thank you for your participation in the ClinSeq™ study! Your involvement and enthusiasm are very important to the success of our study.

Thank you again for your participation in this groundbreaking study,

Leslie Biesecker, M.D.
Principal Investigator
Chief, Genetic Disease Research Branch
NHGRI

Featured Story:

A ClinSeq™ participant's personal experience

Every ClinSeq™ participant has a unique story about their involvement with this remarkable study, including how they heard about it, why they want to participate, what they hope to learn, and what they will learn. In this second edition of the newsletter, we want to introduce you to Dave, a participant whose ClinSeq™ experience so far has been nothing short of life changing.

Dave is an active 55 year old. He works at the National Institute of Standards and Technology and also runs his own consulting business,. He heard about the study through his wife, who saw the ClinSeq™ ad for healthy volunteers in Washington Post's Health section. "You have a history of heart disease in your family," she said to him. "You should do this."

Even though Dave seemed healthy and kept active, he knew that heart disease ran in his family. "I was pretty sure that genetics are not in my favor, so I had to pay attention to it," said Dave. His father had triple bypass surgery at the age of 54. Sadly, he later passed away from a second heart attack at 59. Also, there were members of both the maternal and paternal sides of Dave's family who passed away at an early age from heart disease.

Conscious of the age his father experienced a first heart attack, Dave knew the importance of keeping up with his health. "The thing that I had hoped for was that being active, certainly more active than my father, would be enough to maybe postpone some of the issues my father went through," he said.

Dave enrolled in the ClinSeq™ study in early 2008. "The information collected was phenomenal," he said. "The people I spoke with were very professional, skilled and knowledgeable about what they are doing."
Shortly after his initial visit, Dave received his clinical report. He was taken aback at the results. "Pure shock" is how he described his reaction to the findings. "I remember reading the results and saying, 'What? How is that possible?' The calcium score read 1,118!" Dave began to research this data on the web and found out that his score was in the 90th centile range, meaning

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that he had a higher calcium score than 90% of men his age. "It basically said that if you're over 400, you should be talking to a cardiologist right now. Not only was I above 400, I was way above 400." With his strong family history of heart disease, along with his high calcium score, Dave knew to immediately consult his primary care physician.

In turn, Dave's physician reviewed the results and referred him to a cardiologist. In early April 2008, Dave visited the cardiologist who arranged for Dave to take a diagnostic exam, called a nuclear stress test. Next, he was sent for a heart catheterization procedure at Washington Hospital Center. The heart catheterization

"I'd like to know how traceable the indicator is for heart problems in the genome."
-Dave

showed that 5 of Dave's arteries were 80% blocked. The next day, on May 13th, 2008, Dave underwent sextuple bypass surgery.

This sudden series of events marked the turning point in Dave's health. Dave spent a total of 3 ½ days in the hospital following bypass surgery. That was once he achieved the discharge criterion of being able to walk for 15 minutes, 4 times a day. Then, about 4 weeks out of the hospital, Dave started the cardiac rehab program at Montgomery General Hospital. "I went for 3 times a week for an hour a day," he said.

Dave's perspective on this is remarkably positive. "The nice thing about all this was they found this before I had a heart attack," he said. "So cardiac rehab was a lot easier than it would have been for someone whose heart had to heal."

By August, Dave was able to resume a normal, active schedule, with some minor changes in his lifestyle — including in his diet. "My cardiologist strongly recommended I move to a Mediterranean diet," he said, adding that such a diet includes things he likes, such as fish and chicken. "Things I do miss are the cheese and ice cream. But if that's what I have to give up to stick around a while, then I can do that."

For physical activity, Dave has returned to what he did before undergoing bypass surgery. He umpires high school field hockey four times a week and has gone back to sailing. He even plans to return to playing indoor hockey during the winter months.

Dave's curiosity about genetics and coronary artery disease is heightened as a result of participating in the ClinSeq™ study. "I'd like to know how traceable the indicator is for heart problems in the genome." His own medical status, though, remains the most compelling source of questions it seems. "Is there something I could have done to prevent this, knowing that an indicator was there? What do I need to tell my brother/son if they are at the same risk level as I am at? I want to learn more about the biology of how so much calcium got there."

Does the ClinSeq™ study offer any other genetic insights for Dave? "I'll take anything!" is his eager response to this question. "I am curious to see everything there is to know in the genome!"

If you have a story that you would like to share with us, please email Stephanie Brooks at ClinSeq@mail.nih.gov. We will consider featuring your story in future editions of our newsletter.

ClinSeq™ News

What is the latest on the ClinSeq™ project?

Currently, our focus is still on genes related to heart disease. We have selected about 220 genes for our "gene list" up until now. More genes will continue to be added to our "gene list". At this point, we are selecting genes that play a role in heart function and disease. In the future, we will select other genes related to other conditions. We will keep you informed about future genes and conditions.

Have there been any results yet?
Since the last newsletter we have identified medically important gene changes in several more participants who have high levels of cholesterol, bringing the total number to six participants. These are described below in a special section on ClinSeq™ DNA results update.

Current Enrollment

By Stephanie Brooks, BS
ClinSeq™ Research Assistant

We are currently looking for participants with a history of heart disease (including heart attacks, stents, and bypass surgery) or diabetes. These individuals should also be between the ages of 45 and 65, live in the metropolitan DC or Baltimore area, a non-smoker for the last year, have a primary care physician, and do not have a first degree relative already participating in the study. Our current enrollment is at around 625 and we are looking to enroll 1,000 participants.

If you have friends or spouses who are interested in participating, and meet the criteria, please ask them to call (301) 443-6160. Also, we have updated our ClinSeq™ website to include a video about the ClinSeq™ experience! To view the video, go to http://www.genome.gov/clinseq

Is your phone number changing? Are you relocating?

If your phone number(s) or address changes, please let us know. You can call (301) 443-6160 or e-mail ClinSeq@mail.nih.gov. We need to have your up-to-date contact information so that we can share the latest ClinSeqTM information with you and let you know when genetic results become available for you.

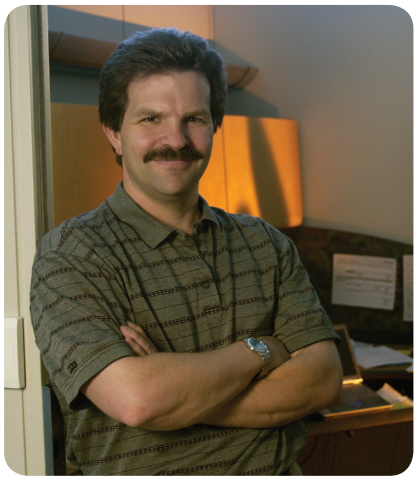
Do you have questions or need to contact us?

- *If you have questions about the study, need to update your contact information, or would like to refer a participant, please call Stephanie Brooks (Research Assistant) or Riley Cooper-McCann (Research Assistant) (301) 443-6160.*

- *If you have questions about your clinical test results (including your echocardiogram, ECG, CT scan, and lab results), please contact Paul Gobourne (Nurse Practitioner) at (301) 594-6341.*

Featured ClinSeq™ Associate Investigator

Q & A with Jim Mullikin, PhD



1) What is your position at NIH?

I am an associate investigator and head of the Comparative Genomics Unit within the Genome Technology Branch of the National Human Genome Research Institute. My group develops computer algorithms for sequence analysis.

2) What motivated you to become involved with the ClinSeq™ study?

I have been involved in sequence variation discovery for nearly a decade, with the primary goal to identify many millions of common single nucleotide polymorphisms (SNPs) among human populations. These common SNPs have been useful in many projects, first within the International Haplotype Map Project (HapMap), then later as they were used for genome-wide association studies (GWAS). In fact, these GWAS studies have now resulted in nearly 200 publications linking genetic diseases or traits to specific regions of the genome, with the long term goal of understanding the genetic basis of common disease. The ClinSeq™ study opens up the spectrum of sequence variants to include even private alleles that may be associated with disease, since

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-Jim Mullikin, PhD

we are sequencing a set of genes within each participant with the sensitivity to discover this class of variation. I am fascinated with this rare part of the spectrum of sequence variation because it is drives us into uncharted territory, and is immediately relevant to an individual when a significant alteration is found and confirmed.

3) What are your other research interests?

My education background is in engineering and physics, with an emphasis on computer algorithm development for reducing large volumes of data into scientifically relevant results. Primarily I work collaboratively with many others on a diverse range of research projects. The ClinSeq™ project is actually just one out of many projects of the type we call medical sequencing (MedSeq). Most of these other projects are one tenth to one hundreth the size of ClinSeq™ in terms of total data collected, but each has its own special mix of genomic regions and individuals selected for sequencing. Beyond the MedSeq realm I have research collaborations that include human population genetics history, sequence analysis of DNA extracted Neanderthal bones, whole genome shotgun sequence assembly of other species, and an array of new technology integration efforts. I find all of these fun and exciting projects to work on together with the talented group of researchers in my team and with all those I collaborate.

ClinSeq™ Scientific Updates

As a ClinSeq™ participant, you may be interested to know that the study has been the subject of a number of scientific and medical presentations since the last newsletter.

Cold Spring Harbor Laboratory meeting on Personal Genomes

Cold Spring Harbor is a leading center for genomics and sequencing technology. It is the current home of one of the co-discoverers of the DNA molecule itself, Dr. James Watson. The laboratory had an inaugural meeting on the topic of personal DNA sequencing last fall and Dr. Biesecker presented preliminary results from the ClinSeq™ study. The study was well received and he has already been invited back next year to present a more detailed description of this unique study.

American Society of Human Genetics

The leading international society of human genetics researchers accepted two applications for platform presentations on ClinSeq™. These platform presentation slots are prestigious in that fewer than 5% of submitted applications are presented in this forum. First, Ms. Flavia Facio presented preliminary results of the qualitative interviews that many of you participated in that addressed your motivations and interests that led you to want to participate in the ClinSeq™ study. Researchers are very interested in your motivations and expectations as this ground breaking research is unfamiliar to most researchers. They are eager to learn why you enrolled and what you hope to be informed about regarding the results. We will present more details about this in a subsequent newsletter, but early indications show that about half of you indicated altruism as a primary motivator and about half indicated that you hoped we would discover some genetic basis for a disorder or trait that ran in your family. Dr. Biesecker presented a second platform presentation on the design and rationale behind the study and the progress of the sequencing efforts. The human genetics

community is very interested in the study and eager to adopt some of our approaches and processes.

Society of Behavioral Medicine
This international society is comprised of researchers who study, among many other topics, health behavior and genetic testing. A more detailed analysis of the motivations and expectations data described above was presented at the annual international meeting by Ms. Barbara Biesecker, a ClinSeq™ collaborator in the NHGRI Social and Behavioral Research Branch.

ClinSeq™ DNA results update
The ClinSeq™ DNA sequencing results are being generated at a truly phenomenal rate. So far, we have generated more than 850,000,000 base pairs of DNA sequence, which we believe to be the largest amount of DNA sequencing ever performed on a patient cohort like ClinSeq™. The generation of such huge amounts of DNA sequence presents both challenges and opportunities. The challenges include issues of data storage and more imprortantly, data interpretation.

We continue to detect clinically important genetic variants in the ClinSeq™ patient volunteers. As of this writing, we have detected seven individuals who have the disorder called familial hypercholesterolemia. This is an uncommon, but more serious, type of high cholesterol, than that which is common in the population. It is exactly the kind of disorder that we are excited about detecting because although it is serious and can shorten life expectancy (due to it causing early heart attacks or strokes) it is readily treatable and with effective treatment, patients can live a healthy and normal lifespan. It affects about 1 in 500 persons in the general population, but surprisingly, we have detected it in 8 out of fewer than 300 samples that we have sequenced so far. This means that this disorder is more than 10 times more common in the ClinSeq™cohort than it is in the general population. We suspect that this is because individuals with familial hypercholesterolemaia are joining the study preferentially, either because they or their doctors suspect they may have this disorder and for one reason or another, the genetic testing has been difficult for them to access outside of the study. What is also remarkable about these seven ClinSeq™ patients is that their family trees or family histories have, in total, nearly 100 more potentially affected people, most of whom have not been diagnosed with familial hypercholesterolemia. Many of these 100 undiagnosed relatives of ClinSeq™ patients are not currently receiving complete treatment for this disorder. We are currently working hard with the affected ClinSeq™ participants to identify and test their family members and help them to institute effective treatment for their disorder.

The exciting thing about these early results is that we have the opportunity to detect and effectively treat dozens of people, whose lives can be significantly extended by this type of diagnosis and treatment. It exemplifies a potentially powerful aspect of an approach to medical care that has been called "personalized medicine" or "individualized medicine". By this we mean that medicine and medical care may be more effective if we can precisely identify the factors that significantly modify health risks in individual patients and apply a focused and intensive treatment regimen to that patient. The ClinSeq™ study that you have joined is a pilot to develop the infrastructure for a new kind of medical care that is focused on the patients who can benefit greatly from this approach to medical care.

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For more information about the ClinSeq™ project, visit
www.genome.gov/ClinSeq