

Medscape Medical News from:

The Future of Genomic Medicine (FGM) III

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The Genetics of Health and Aging: An Expert Interview With Sarah S. Murray, PhD

Jacquelyn K. Beals, PhD

March 23, 2010 — *Editor's note: Current genetics research has identified several "canonical" pathways that influence aging. These involve dietary restriction, insulin signaling, and mitochondrial energy processes. This past fall, through a series of events they describe as serendipitous, researchers realized that the homolog of Drosophila gene 4E-BP, which extends lifespan in fruit flies, is a significant gene at a choke-point of 3 pathways influencing human lifespan.*

In an interview with Medscape Pathology, Sarah S. Murray, PhD, moderator of the session on Genomics of Health and Aging, and director of genetics, Scripps Genomic Medicine, at Scripps Translational Science Institute in La Jolla, California, discusses this and other advances in our understanding of genes that influence lifespan, as presented at The Future of Genomic Medicine (FGM) III, cosponsored by Scripps and the J. Craig Venter Institute, and held March 5 and 6 in San Diego, California.

Medscape: This is the third year of the FGM conference. As someone who has worked on planning the conference, how has it evolved during this time, in terms of the selection of topics and the direction you see the field going?

Dr. Murray: I think the meeting is a combination of our picking topics and where the field is. Last year we had sessions that were very technology-focused, but that's where the state of the field was at the time. All of these next-generation sequencing technologies were coming onto the scene and gaining momentum. As a tool for doing research in genomics, we thought it was important to highlight this and to have people become familiar with these technologies.

This year we tried to be more applied. How to use these technologies practically is really the big thing, and obviously what came out is that we're using them to sequence primarily cancer genomes, and for whole-genome sequencing in other areas as well. I think this is a natural progression from being focused on technology to changing how it's applied. Also, last year was more of a GWAS [genome-wide association studies] era. My particular talk last year was on areas where there were holes in our knowledge, pointing out the great strides GWAS studies have made, but also where some of the limitations are. I think now the field is shifting focus into sequencing, as well, to help fill some of those holes, going after more rare variation and its role in disease.

Medscape: What were some of the highlights — most interesting, or exciting, or what generated the most discussion — at your Genomics of Health and Aging session?

Dr. Murray: One of the themes throughout the session was the 3 main prongs of what Andy Dillin [PhD, Howard Hughes Medical Institute and Salk Institute, La Jolla] referred to as the "canonical" pathways for lifespan: insulin signaling, dietary restriction (essentially restricted caloric intake), and the mitochondria. Andy did a great job talking about the insulin growth factors pathway and the good models there for Alzheimer's disease in *Caenorhabditis elegans* and in the mouse, and Nir Barzilai [MD, Albert Einstein College of Medicine, Bronx, New York] touched on that in his talk about the human population he works with.

Eric Topol [MD, director of the Scripps Translational Science Institute and chief academic officer for Scripps Health, in La Jolla] tied it in with a genome-wide association study, and Doug Wallace [PhD, University of California, Irvine School of Medicine] talked about mitochondria and aging. He really touched on that third prong. They all complemented each other and drove home this main area of interest for aging and lifespan — healthy aging in particular.

Medscape: Could you give a thumbnail sketch of how each of these 3 prongs affects healthy aging?

Dr. Murray: I'm not an expert in any of these areas, but Andy [Dillin] essentially talked about the role of IGF1R in the insulin growth factor pathway in Alzheimer's disease. What he showed is that decreased signaling slowed the onset of Alzheimer's disease in his models. That was a really nice study, not so much about healthy aging but is relevant to age-related disease.

In terms of the mitochondrial angle, it all has to do with energy, reactive oxygen species, apoptosis and cell death, and the regulation of oxidative stress and homeostasis — the whole process and cycle of maintaining that proper balance. If things go wrong, then you can have more damage or it's not as efficient, and you have more oxidative stress.

Essentially, Doug Wallace talked about what he termed the "energome," showing lots of pathways, a very intricate cycle, and pointed out how things that stress and alter these pathways are related to the whole aging process.

For dietary restriction, Eric Topol is the one who touched on that the most, and it's really interesting. Some work — not our work but work that was published in *Science* [2009;325:201-204] — was this prospective study on rhesus monkeys in which essentially one group had caloric restriction and the other one didn't. The ones that did not have caloric restriction had a much higher percent of age-related disease, including dementia and cardiovascular disease, pretty much all the normal age-related diseases.

If you look at the pictures of the 2 monkeys, the one with caloric restriction looks very healthy and, of course, thin, and the other one looks much older. But there were quotes from someone in *The New York Times*, basically saying that the monkey on the caloric-restricted diet just looked agitated. He was starving his whole life so he looked really healthy, but "Is it worth it?" sort of thing.

I think the take-home message is that there's some process in caloric restriction that's related to this [target of rapamycin] pathway and the genes that we've honed in on from our genome-wide association studies involved in this pathway. If we can understand what caloric restriction does and how that is involved in reducing the aging process, that obviously provides great clues into the whole process of healthy aging. It's a nice story, and it seems to be coming together if our results actually hold up.

Medscape: Did I hear about some sort of "magic" gene that seems to be at the intersection of several aging-related pathways?

Dr. Murray: Right. That's this gene that we've identified through genome-wide association studies; *4E-BP* is actually the homolog in *Drosophila*. The human version is *EIF4EBP3*. We found a healthy aging-associated region on chromosome 5, the region where this gene is located, and because it's the homolog of the gene in *Drosophila*, we know this gene is at the choke-point, so to speak, of the major pathways known to be involved with aging processes. That's why we're really excited about it.

Medscape: Did this just develop in the past year or so?

Dr. Murray: Yes. People have been working on this for a long time, but it was actually great serendipity. I talked about our genome-wide association study at the American Society for Human Genetics meeting last October, when the meeting was in Hawaii. At the time, there were a bunch of genes under the region, and the most associated [single-nucleotide polymorphism] was in the intron of another gene that pretty much overlaps with the one I just mentioned. But around the same time, a paper in *Cell* (2009;139:149-160) came out in which they were talking about this gene in *Drosophila*, and how it actually extends the lifespan upon dietary restriction in *Drosophila* by enhancing mitochondrial activity. So all of a sudden we just made this connection. The paper just came out in *Cell*, and this gene is sitting right under the region we've identified through the genome-wide association study. It makes, obviously, a terrific story, so that's how all this converged.

Medscape: Where do you think it's going to go from here? Are people looking for human applications, other than telling people "don't eat too much and control your blood sugar"?

Dr. Murray: People don't want to know that they should cut back on calories. Where it goes from here [depends on whether] we can really start to understand what is unique to a healthy aging population — what we call "welderly". I think what all this helps with is gaining insight in biology. If we can start to understand what is unique to [the welderly] — how this is influencing the whole healthy aging process — then the ultimate goal is to be able to target that for interventional therapeutics. We think that in other people, who may *not* be naturally protected by these great protective factors, somehow you could help prevent the onset of disease by targeting these pathways.

All these diseases that we study are complex disease traits, so it's not going to be an all or none kind of thing. I think what we're looking for are clues to what are likely to be protective factors. Our theory is that our healthy aging group probably has roughly the same spectrum of deleterious alleles as most people in the population, but they have protective factors that help prevent them from becoming sick. They potentially have better immune response, they have better repair mechanisms, they have something that allows them to kind

of ward off disease, so this is one clue into that. This [gene] probably plays a role — it's not going to be the only role, but so far the evidence is pointing this way, that this could potentially be a really exciting finding. In all these diseases we find clues, and it helps provide another piece of the puzzle, but nothing's been fully explained yet.

Medscape: You had a very full weekend with the Scripps conference, and I heard you had to dash off to give another talk the following Monday. Could you say something about the topics you talked about at both conferences?

Dr. Murray: I spoke at the [FGM] conference on Friday, and talked essentially about where the field is, with being able to do risk prediction based primarily on markers from genome-wide association studies. The take-home message is that there are obviously a lot of limitations, but there are cases where there is some utility. The hope is that as we're starting to identify genetic risk factors that actually have larger effects, and we are starting to see those. The presumption is that the prediction will improve.

The talk I gave Monday was at the Gordon [Research] Conference [held March 7 to 12 in Ventura, California], which was about the biology [and pathobiology] of the cornea. This is out of my area of research, but they wanted someone to come and talk about genetics, so I basically talked about genome-wide association studies and sequencing, and what we've learned, and how you do it. I gave age-related macular degeneration as an example, because that's actually one of the diseases that has had great success with genome-wide association studies, with some complement factor H and a few other genes implicated that actually account for much of the genetic contribution for macular degeneration. The great poster child of successful GWAS. That wasn't my work, but I mentioned it as an eye-related example.

Medscape: Is there anything you'd like to say to *Medscape Pathology* readers, like: "Be interested in genomic medicine"?

Dr. Murray: I think the reason why this conference is so well received is that there's a really nice balance between clinicians and researchers. It has different fields, while [the American Society of Human Genetics] has more genetics-focused meetings. So even the sequencing talks, I thought, were fantastic and focused on relevant "what does this mean to you" kind of things. There were some technical details, because that's still where the field is, but it's a nice mix and I think it was well received. I'm hoping people weren't intimidated, that they actually got a lot out of it, learned a lot, and are excited about what's going on in the field of genomic medicine.

Dr. Murray has disclosed no relevant financial relationships; she is a member of the Scripps research group, and a conference organizer.

Authors and Disclosures

Journalist

Jacquelyn K. Beals, PhD

Jacqueline K. Beals, PhD, is a freelance writer for Medscape.

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