Beautiful Piles of Bones: An Interview with 2017 Genetics Society of America Medal Recipient David M. Kingsley

David M. Kingsley
Department of Developmental Biology and Howard Hughes Medical Institute, Stanford University School of Medicine, California 94305-5329

The Genetics Society of America Medal is awarded to an individual for outstanding contributions to the field of genetics in the last 15 years. Recipients of the GSA Medal are recognized for elegant and highly meaningful contributions to modern genetics, exemplifying the ingenuity of GSA membership. The 2017 recipient is David M. Kingsley, whose work in mouse, sticklebacks, and humans has shifted paradigms about how vertebrates evolve. Kingsley first fell in love with genetics in graduate school, where he worked on receptor mediated endocytosis with Monty Krieger. In his postdoctoral training he was able to unite genetics with his first scientific love: vertebrate morphology. He joined the group of Neal Copeland and Nancy Jenkins, where he led efforts to map the classical mouse skeletal mutation *short ear*. Convinced that experimental genetics had a unique power to reveal the inner workings of evolution, Kingsley then established the stickleback fish as an extraordinarily productive model of quantitative trait evolution in wild species. He and his colleagues revealed many important insights, including the discoveries that major morphological differences can map to key loci with large effects, that regulatory changes in essential developmental control genes have produced advantageous new traits, and that nature has selected the same genes over and over again to drive the stickleback's skeletal evolution. Recently, Kingsley's group has been using these lessons to reveal more about how our own species evolved.

This is an abridged version of the interview. The full interview is available on the *Genes to Genomes* blog, at genestogenomes.org/kingsley/.

What inspired you to become a scientist?

My dad died of cancer when he was 34. As a little kid I was aware that you don't know how long you have left, and I grew up wanting to make sure I spent the time I have doing something interesting and important. I thought that tackling age-old mysteries about life's origin and mechanisms was a good way to spend my life.

What did you learn from your first mentors?

I was a kid who loved dinosaurs and skeletons. That interest was nurtured by a great high school teacher, Jack Koch at Roosevelt High School in Des Moines, Iowa. In his advanced biology class we memorized the names of every bone and muscle in the cat and human skeleton. A lot of people hated it, but I loved it because you could see so much about the function and lifestyle of the organisms from the size and shapes and patterns of bones.

In graduate school I fell in love with the power of genetics. I had a set of teachers at MIT, including David Botstein and Monty Krieger, who helped me learn that with genetics you didn't have to assume anything about the answer to your question. You didn't have guess that you were looking for a particular type of molecule or anything like that. Genetics was an algorithm that would take you to the key components controlling a biological system no matter what they were.

Why did you choose to work on the *short ear* gene?

Vertebrate genetics takes a long time, so you should pick your problem carefully. I didn't want to pick something that was better studied in bacteria, yeast, or powerful invertebrate systems. The skeleton was perfect; it's the defining feature of vertebrates. It also plays such an important role in animals' external appearance that many classic mutants had already been picked up in simple morphological screens.

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After World War II there had been a lot of interest in the effects of radiation on the mammalian germline, and there were two big mouse forward mutation experiments in the UK and US. They both used a test strain carrying seven homozygous recessive mutations with visible phenotypes. These were six pigment mutations and *short ear*. Millions of wild type mice were mutagenized and crossed with the test strain to measure the rate that new alleles were recovered at any of the seven loci. As a result, there were lots of newly induced mutations, including a whole set of deficiency chromosomes that took out both *short ear* and one of the closely linked pigmentation loci. We essentially had the equivalent of a *Drosophila* genetics playground for this particular region of the mouse genome!

What did you learn from the *short ear* project?

It took ~5 years to do the chromosome walk in the region, and I was already an assistant professor by the time we eventually isolated the gene for this classic skeletal trait. But it was incredibly gratifying. The gene controlling skeletal morphology encoded a secreted signal already named a "bone morphogenetic protein" (BMP). It had been named by biochemists who found that if you took an adult bone and ground it into powder and injected it under the skin of an animal, there was some magic ingredient that could generate a brand new bone at the site of implantation.

The short ear mice provided the first genetic evidence that BMPs were the endogenous signals that vertebrates were using to set the form and pattern of skeletal structures. The large collection of *short ear* mutations later helped us to identify a whole series of modular, remarkably specific enhancers controlling different aspects of skeletal morphology. For someone originally interested in those beautiful piles of bones, to be able to break down their shapes into the expression patterns of secreted signaling molecules was an incredibly satisfying answer.

Why did you choose sticklebacks?

If you can find a way to turn old biological problems into genetics problems, then you can often find the answers to even intractable questions. A brave postdoc, Katie Peichel, and I spent a really fun summer in 1998 figuring out how to turn classic evolutionary questions into a genetics problem. We wanted to identify the number and type of genes and mutations that control species differences in nature. We went around talking to biologists, reading all kinds of books, looking for very young species with recently evolved and dramatic skeletal differences that could still be crossed in the laboratory. Somewhere in the middle of that summer I found a great book chapter by Mike Bell of Stonybrook University talking about all the cool skeletal traits that had evolved in sticklebacks after the end of the last Ice Age. There was a remarkable previous literature on stickleback morphology, ecology, and behavior in new freshwater streams and lakes. And new forms had evolved not just once but thousands of times. It was like nature had set off a replicate series of evolution experiments 10,000 years ago, producing new forms over and over again.

What did you learn about the repeatability of evolution?

I had a debate with a fellow faculty member when I started the project because he thought the project was not worth doing. It would just turn out to be postage stamp collecting, and there wouldn't be any generality.

At the time, we didn't have evidence one way or another. But my best reply was: how do you know? That was the great thing about genetics—it would tell you the answer no matter what the answer is. We started crossing these fish with huge skeletal differences. And if you compared the results from crosses done in different lakes, it turned out the very same chromosome regions were being used over and over again in different populations.

We've subsequently taken lots of traits down to genes and molecules. We've found that the key signals and transcription factors that developmental biologists have been studying for years turn out to be the same molecules that nature is using to redesign anatomical features. For example, although we didn't set out to test any particular candidate genes, the genetic data showed us that some of those stickleback skeletal traits are controlled by the same kinds of bone morphogenetic proteins that we found in mouse.

How does the stickleback work connect with your studies of human evolution?

We're interested in *why* particular genes are reused throughout evolution, and we're also interested in applying the patterns we've found in sticklebacks to the evolution of ourselves. We've found that classic traits in people, like blond hair color, or height, are evolving in humans using the same types of key control genes and regulatory mutations we have found in fish. And, unlike rare genetic diseases, there are derived alleles at these human loci where a large fraction of the population carry the selected version. In some cases, the selected alleles may actually alter susceptibility to late onset diseases like skin cancer or arthritis. It's not a huge effect, maybe 1.3- to 1.8-fold. But when an allele slightly increases risk of a disease and is carried by a few billion people through selection, then suddenly you find an awful lot of the burden of a common human disease is controlled by our own evolutionary history. We're now going back and forth between humans and the patterns we see in fish. We thought it might take us 50 years to get enough examples to pull out general principles, but it turned out to be much faster that.