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An interview with Michael Nachman

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Michael Nachman (right) and Antonio Barbadilla (left) last June at the UAB

Michael Nachman, Professor of Integrative Biology and Director of the Museum of Vertebrate Zoology at the University of California, Berkeley, is one of the most relevant evolutionary biologists of our time. His research covers areas such as population genetics, evolution, genomics, ecology, and mammalian evolution. With more than 150 articles of high impact in Evolutionary Biology, he has provided new significant insights on how organisms adapt to their environment and how new species arise. His main research organism is the house mouse. Thanks to his work, the house mouse is, in fact, one of the model organisms of evolutionary population genetics, rivaling the Drosophila model. A leitmotif in Michael's research is the idea of integration in the broad sense. His work exemplifies the integration of molecular genetics with ecological and evolutionary theory; field and laboratory studies; experimental and theoretical/bioinformatics approaches; large multi-omics datasets. Michael is the archetype of the total evolutionary biologist. One of Michael's best-known studies deals with the genetic basis of adaptive melanism in pocket mice, which has become a textbook example of natural selection in action. He has received numerous awards and recognitions for his scientific contributions, reflecting the deep and lasting impact of his research.

Michael recently spent a sabbatical in Josefa González's group at the Institute of

Evolutionary Biology in Barcelona. During his stay he gave numerous lectures at congresses, conferences and seminars held in Spain, dealing with his most recent research on the genomic basis of environmental adaptation in house mice. I invited him to give the closing lecture of the biosciences conference that is held annually in our faculty of biosciences at the UAB. Michael generously accepted, and also agreed to participate in this interview for eVOLUCIÓN.

1st Q: An inevitable question to start our interview, what prompted you to dedicate yourself to research in evolutionary biology?

I was lucky to have been raised in a family that spent a lot of time outdoors. We went camping during the summers and visited many of the gorgeous national parks in western North America. We also had a house full of pets as I was growing up including a dog, cats, a rabbit, a tortoise, hamsters, fish, and a pet cockatiel. So, I grew up around animals. In college, I was exposed to the wonderful diversity of plants and animals through classes that took students into the field, including mammalogy, ornithology, invertebrate zoology, and systematic botany. During this time, I spent summers as a naturalist ranger at Yosemite National Park. So, I guess I naturally developed a love of nature and biodiversity. Research in evolutionary biology just seemed like a natural outgrowth of these experiences.

2nd Q: Why did you choose the house mouse to study the genomic basis of environmental adaptation? What evolutionary issues can be better addressed with this animal model?

I started my research career studying the South American marsh rat, *Holochilus brasiliensis*. This was the focus of my PhD thesis. This species is unusual in possessing a high degree of chromosomal polymorphism. I travelled to south America three times to collect these animals, and I brought them back alive to the University of Michigan where I established a breeding colony. The biological questions were fascinating, but the species was very difficult to work with. My interest in chromosomal evolution led me to the house mouse, *Mus musculus*, which also exhibits considerable chromosomal variation. However, house mice are easy to collect and breed in the lab. I quickly became enamored with the power of model organisms. Even in the 1990's we had a decent genetic map, and hundreds of mutations had been characterized. By 2002 we had

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a complete genome sequence and a deep database of genetic and phenotypic variation. This makes it possible to study the genetic basis of adaptation for complex traits in a way that would be difficult or impossible with most organisms. In addition, house mice have recently colonized many new environments and have adapted quickly through changes in morphology, physiology, and behavior, making them a useful model for studying evolutionary changes over short timescales.

3rd Q: By studying the phenotypic and genetic changes in 186 house mice collected across North and South America, you found plenty of evidence of recent adaptation to their living different environments. What does it tell us about the ability of mice to adapt to new environments?

Most fundamentally, it tells us that evolution can happen quickly. House mice were introduced to the Americas by Europeans during the last few hundred years. In this short amount of evolutionary time, mice have evolved to be distinct in different geographic regions. For example, mice from Canada are 50% larger than mice from the equator. These differences persist in a common laboratory environment, indicating that they have a genetic basis. Even though we call them house mice, most mice don't live in houses. They live in barns and areas where grain is stored and are therefore exposed to the elements. Winters in Edmonton, Canada are very different from winters in Manaus, Brazil! These climatic differences imposed strong selection and resulted in the differences that we see today among mice from different environments.

4th Q: Can the observed ability of mice to adapt to new environments in a very short evolutionary time be extrapolated to the rest of rodents and/or mammal species or even to other taxonomic classes?

Rapid evolution is possible when populations harbor extensive standing genetic variation. The amount of variation depends, in part, on the demographic history of popula-

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tions. Populations that have experienced a prolonged bottleneck may be less equipped to respond to selection. This is a concern for many threatened or endangered species. But for species that have large effective population sizes, a lot of genetic variation, and short generation times, rapid evolution is often possible. In his famous 1974 book, *The genetic basis of evolutionary change*, Lewontin remarked that there is no aspect of the phenotype of *Drosophila* which cannot be selected. This is surely because of the large amount of genetic variation present in most natural populations.

5th Q: What is the role of standing genetic variation versus new mutations for the adaptation to new environmental in mice?

Most of the statistical "signatures of selection" that we see in the genome of house mice are consistent with selection acting on standing variation rather than on new mutations. This makes sense because the timeframe in question is very short, probably too short for new mutations to play a major role.

6th Q: With respect to the difference between Quantitative Trait Loci (QTL) vs Mendelian traits, what is the main genetic target of the inferred adaptive changes: the quantitative traits, based on polygenes, or the Mendelian traits, based on genes with major phenotypic effect?

Most of the traits that we are studying now are highly polygenic. This is by design. Twenty years ago, my lab studied variation in the color of pocket mice that live on light and dark rocks (Nachman et al. 2003. *Proc. Nat. Acad. Sci. USA* 100: 5268-5273). At that time, we chose to study melanism because it was a very simple trait. When we started that work in the late 1990's, there were no genome sequences available. We were lucky and discovered that a single gene – *Mc1r* – was responsible for differences in color. That work led to similar work on a variety of traits and organisms, including beautiful studies of melanism in deer mice by my former postdoc, Hopi Hoekstra. The field of evolutionary biology now has dozens or even hundreds of examples of the

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genetic basis of adaptation for simple traits controlled by one or a few genes. Yet most of evolution involves quantitative traits, where many genes each contribute a small amount of variation. We still have a poor understanding of the genetic details of how such traits evolve. House mice provide a good model for this problem.

7th Q: How does the population structure of the house mouse impact its ability to adapt to environmental changes? Do migration and gene flow between populations facilitate or hinder adaptation?

On their own, house mice disperse short distances. However, long-distance migration can be facilitated by human transport. In general, though, gene flow among house mouse populations appears to be low over the geographic scale in which we see substantial climatic variation. In other words, selection is probably a stronger force than migration. There is no evidence that migration hinders adaptation. Migration may have facilitated adaptation in the sense that the beneficial alleles that have risen to high frequency in the Americas were introduced by migrants from Europe.

8th Q: As mentioned above, a common theme of your research is the integration of evolutionary approaches. Is the study of the Genotype-Phenotype-Fitness (GPF) connection the best current approach to understanding selection and adaptation? How does the evo-devo approach to evolutionary biology integrate with the GPF approach?

Integrating development into studies of evolution is critical. For example, we found that house mice that are adapted to cold environments have shorter tails than house mice that are adapted to warm environments. This difference is due to differences in the total *number* of tail vertebrae as well as differences in the *length* of individual vertebrae. Both of these traits (number and length) arise during development. The number of vertebrae is determined around day 12 of embryogenesis, while the length of the tail vertebrae is

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largely determined in the first few weeks of life. To fully understand how these differences arise we are studying gene expression in the developing tail at these different times.

9th Q: A main subject in your research is that of phenotypic plasticity vs adaptive selection. How are the two concepts related in the real world? Does phenotypic plasticity facilitate or hinder adaptation?

This is a wonderful question! And it is still unresolved. In general, phenotypic plasticity which brings a population closer to the optimum may facilitate the colonization of new environments and subsequent adaptation. Conversely, plasticity which reduces fitness in a new environment may make it harder for organisms to invade that environment. We raised warm-adapted (long-tailed) and cold-adapted (short-tailed) mice in warm and cold laboratory environments and we found that all mice grew shorter tails in cold environments! This shows us that when mice invade a new, cold environment, they exhibit a plastic response that presumably is beneficial since short-tailed mice lose less heat. In addition to that plastic response, we found a strong genetic component to differences in tail length between warm-adapted and cold-adapted mice. So, in this particular case, phenotypic plasticity appears to facilitate adaptation.

10th Q: Another main theme in your research is that of evolutionary convergence (repeatability) vs uniqueness in evolution. What can you tell us about the genomic evidence of evolutionary convergence in the adaptation of house mice to similar environments in geographically separated populations? What is the deep level of convergent adaptation: phenotypic and/or genetic, and what is their evolutionary significance?

House mice have invaded cold environments at least three times independently in the Americas, once in western North America, once in eastern North America, and once in South America. This allows us to study whether evolution is repeatable by sampling mice across these three large geographic areas. At the level of the phenotype, evolution is repeatable. We found that mice are larger in colder environments in each transect. We also found convergent changes at the level of the genes. For example, there are many alleles that in-

crease in frequency from the equator to Tierra del Fuego, the southern tip of South America. Those same alleles also increase in frequency in northern latitudes. Thus, we see similar patterns in both the northern and southern hemispheres. This is perhaps not surprising since selection probably acted on the same ancestral pool of genetic variation in each case. Repeated evolution like this is also seen in *Drosophila* in the northern and southern hemispheres.

11th Q: What major challenges remain to be addressed in evolutionary biology? Is there a fundamental gap that is not covered by the present evolutionary theory?

There is a parallel between the state of knowledge in evolutionary genetics and the state of knowledge in medical genetics. We know a lot about the genetic basis of adaptation for simple traits, and we know a lot about the genetic basis of monogenic diseases. But most of evolution is due to complex traits, and most of the disease burden is due to complex diseases. In both cases, our understanding of the underlying causes – both genetic and environmental – is still in its infancy. I see this as one of the great challenges in evolutionary biology. Addressing it will require studies of different taxa, both in nature and in the laboratory, in a way that allows us to combine genetics, development, and natural history. To truly understand how organisms evolve, we must study them in their natural environment.

12th Q: And finally, a question especially relevant to our young readers, what advice would you give to the new generations of evolutionary biologists?

The hardest thing to do well in science is to ask the right questions. Go into nature and observe organisms in their environment. Careful observation can lead to interesting questions. It is also essential to read widely, especially the older literature, but think for yourself. The older literature is a wonderful source of ideas and unfinished stories. Finally, follow your heart. There is no substitute for enthusiasm and excitement when doing research.

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