Robert Herbst / GMI Vienna

A conversation with Magnus Nordborg, Vienna

"There's So Much We Can Learn"

Ten years ago, the Austrian Academy of Sciences founded a new Institute for Molecular Plant Science in Vienna. In September, the Gregor-Mendel-Institute will celebrate its grand opening. Prior to the event, Karin Hollricher talked to current director, Magnus Nordborg, about modern plant research and its significance in science.

Lab Times: You are the director of the new Gregor-Mendel-Institute of Plant Molecular Biology in Vienna. What's your interest in plants?

Magnus Nordborg: We would like to unravel how genetic variation translates into phenotypic variation and how this translation depends on the environment. Plants are ideal for this purpose because genetically identical individuals can be grown in replicate in multiple environments. That's not only a fundamental issue for understanding evolution but also has enormous practical implications for agriculture. Our group studies the genotype–phenotype map and wants to set up models to understand quantitative variation and evolution better.

How do you correlate genotype to phenotype?

Magnus Nordborg: We're doing genome-wide association – GWA – mainly in *Arabidopsis*, to find major variants that explain natural variation and adaptation in plants. With these GWA studies we can find genes and map them right away.

For the non-geneticists in our readership: could you please shortly explain how a GWA is done?

Magnus Nordborg: The principle behind GWAs is very simple: ideally, you sequence everyone and then look for correlations between genotype, in the form of sequence-level differences, like SNPs and phenotype. In practice, most GWAs to-date have utilised partial genotypes, e.g. SNP genotypes.

However, human geneticists have not been too successful in identifying disease genes with GWA studies.

Magnus Nordborg: That's right. Or, more correctly, they have not been successful at explaining much of the population-level variation for disease susceptibility. Many genetic variants have been found but, generally, they do not explain much of the variation because they either have small effect, or very low frequency.

"My group will contribute 200 genomes to the 1001 Genomes Project."

Do plants make a difference?

Magnus Nordborg: It's the kind of traits we're analysing that make a difference. We're looking for adaptive traits that are thought to be encoded by major–effect polymorphisms. It's not too complicated to map genes that have big effect, not even in humans. For example, one could easily identify skin colour genes in GWAs. Now we want to map major genes affecting variation and adaptation in plants.

You, and plant biologists from the USA and other European countries, recently published an article describing a genome-wide association study of 107 phenotypes in Arabidopsis thaliana *inbred lines. You identified several common alleles of major effect but you also wrote "..they are also, in many cases, harder to interpret because confounding by complex genetics and population structure make it difficult to distinguish true associations from false". Isn't that exactly what human geneticists are struggling with?*

Magnus Nordborg: No, in the case of humans, people are looking for genes involved in diseases like cancer or heart failure. I think they have difficulties finding such genes or alleles because major alleles causing disease have been selected against in the past. So the alleles people are looking for now are either alleles with small effect or alleles that are very rare. And those are hard to find. In general, disease genes have either no major effect or, if they have major effect, they are not frequent in a given population. That's not true for genes involved in adaption. That's the reason why we can identify adaption genes in a small pool of lines.

Why do you think that adaptive genes are major genes?

Magnus Nordborg: Because adaptive polymorphisms have been maintained by selection, whereas polymorphisms that cause disease, tend to be due to recurrent mutation that is constantly eliminated by selection. For example, many cases of pathogen resistance in plants are due to major-effect polymorphism.

When the pathogen is common, the benefits outweigh any fitness costs and the resistance allele increases in frequency. The resulting increased resistance decreases the frequency of the pathogen, which, in turn, leads to the cost of resistance outweigh-

ing the benefits, so the allele frequency decreases again. And so on. The result is a balanced polymorphism, with both resistance and susceptibility alleles maintained at high frequencies.

Sequence data also indicate that the genomes of Arabidopsis *species differ extremely, so much that Detlef Weigel wrote about the plant's genome, "There's no genome".*

Magnus Nordborg: Of course, there are limitations and most polymorphisms will not have a phenotypic effect. But note that with only 96 inbred lines we were able to map major genes. To identify the genetic variability, the whole genome sequence variation in the genus, we are participating in the 1001 Genomes Project. My group will contribute 200 genomes. The information combined with GWAs in wild strains will reveal alleles responsible for phenotypic diversity, I'm sure!

What adaptive traits are you looking for?

Magnus Nordborg: My group does not work on disease resistance because we do not have the expertise. Instead, we focus on the abiotic environment. We want to figure out what governs who grows where, which genotypes grow in which places. So, we test adaptation to abiotic conditions, such as drought or temperature. We have 16 brand new, highly sophisticated climate chambers with 250 square metres of total shelf space at the GMI. In these chambers we can simulate abiotic conditions very, very accurately and that's important for the definition of the phenotype. For example, when we grew Arabidopsis at 10, 16 and 22 degrees, a quarter of our tested accessions died at 22 degrees. Obviously, plants' natural habitats are different to what we have in the laboratory. Arabidopsis is happy at 10 degrees, the plant is adapted to a more moderate climate. The natural life cycle even involves overwintering as a rosette. And in the new chambers we can simulate that condition for months.

Are you working with Arabidopsis *only?*

Magnus Nordborg: No, we also try to identify genes involved in the variability and adaption of *Aquilegia*. There are great differences between columbine species, especially concerning the flowers that are pollinated by various animals, such as bumble bees, moths or humming birds. We want to find the genes that make the difference, that underlie the co-evolution of flower and specific pollinator. Also, *Aquilegia* is becoming interesting because it is highly diverse. There are 70 species and you can intercross all of them. And we also work on the genetic variability of African Green Monkeys.

> ***"Many of the answers we get are universal, also concerning other organisms."***

Does your work overlap with other groups at your institute?

Magnus Nordborg: Sure. For example, there are some groups working on epigenetics. We would like to find out whether epigenetic variation plays a role in natural variation and they are helping us interpret our results. There's also a lot of overlap in our work on genome size variation. And my group is doing a lot of bioinformatics for other people here.

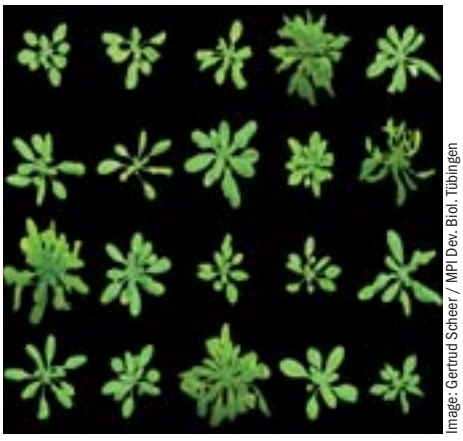

Image: Gertrud Scheer / MPI Dev. Biol. Tübingen

Rosette variation in *Arabidopsis*

Animal research has – for a good reason – various model organisms. Doesn't plant biology need others too?

Magnus Nordborg: Sure, we clearly need models for grasses and trees. There are several coming up. But we can also learn a lot from *Arabidopsis* closest relatives, the Brassicaceae. And indeed, we have other models: maize and rice, for example.

Both were chosen because they are major food crops and also of commercial interest. If you had to choose a new plant model you would not choose maize, would you?

Magnus Nordborg: Certainly not. That is similar to humans: most probably we would not have chosen to work on humans if we weren't human! Scientifically, humans are really bad models. They have an extraordinarily long generation time and you can't manipulate them genetically, can't make transgenics. But we are human…

> ***"A scientist never has enough money"***

The GMI was founded and is financed by the Austrian Academy of Sciences. Do you know why the Academy is investing in basic plant research?

Magnus Nordborg: I'm extremely happy that people have recognised the importance of having basic research in plant biology. On a global scale, plant biology — basic and applied — has been neglected recently. Biomedical researchers were getting much more money and there was a wide-spread notion that hunger was a solved problem. But I have the feeling that in 2007, when some countries suffered from food shortages, politicians began to pay more attention to plant biology.

Well, food resources are important – but Arabidopsis is not really known as a major crop plant.

Magnus Nordborg: That's true but since *Arabidopsis* has become the model organism in the front line of plant biology, one doesn't need to argue too much when it comes to funding within the money allocated for plant biology. Not funding plant research is a mistake – at least in my eyes. Curiosity-driven basic research in plant biology is very, very important. And so, I'd like to stress that it was a very good decision to set up the Gregor-Mendel-Institute. There's so much we can learn. I'm a geneticist having chosen plants as a model for adaptation. But many of the questions I raise and many of the answers we get are universal, also concerning other organisms.

Are you satisfied with the institute's funding?

Magnus Nordborg: (laughs): A scientist never has enough money! But frankly speaking, I wouldn't have moved to Austria without having been guaranteed sufficient funding for making the institute internationally competitive.

Your institute's name should be "Programme". Can you fill Gregor Mendel's footsteps?

Magnus Nordborg: (laughs): No, I suppose not. Clearly Mendel's discovery was one of the major scientific achievements of the 19th century. I do not expect us to achieve similar "breakthroughs of the century" but we'll do our best. Our ambition is to do world class research. And that I can guarantee.

INTERVIEW: KARIN HOLLRICHER