Why I Love Genetics: Essay on Occasion of Being Awarded the GSA Medal 2016

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The Genetics Society of America (GSA) 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, and exemplify the ingenuity of GSA membership.

The 2016 recipient is Detlef Weigel, whose contributions include the identification of the molecular basis for floral patterning; the determination of mechanisms for flowering time; and elucidation of genetic tradeoffs between growth and immunity in natural populations. Notably, his group identified the gene for florigen, a compound made in leaves that induces flowering. Throughout these investigations, Weigel developed multiple resources for the plant genetics community, including activation tagging to create gain-of-function mutants; gathering data and creating a web interface for AtGenExpress, a gene expression atlas for *Arabidopsis*; and jumpstarting the 1001 Genomes project of *Arabidopsis thaliana*.

Detlef's deep rooted understanding of genetics and his technological creativity both drives and serves an exceptionally broad and fearless palette of interesting and important biology.

—Jeff Dangl, University of North Carolina at Chapel Hill / Howard Hughes Medical Institute

My dad introduced me to biology. He was a birder, and our district's "stork father," looking after the local stork population: repairing and building nests on barns, and counting and ringing fledglings. Biology was thus a natural favorite for me, and I knew early on that this is what I wanted to study in university. My other two favorites in school were math and Latin because of their logic and abstract formalism (obvious for math, but it also applies to Latin grammar). It is this formalism that made me fall in love with the biological discipline of genetics, to which the late José Campos-Ortega introduced me when I was an undergraduate at the University of Cologne. Muller's classification of alleles into amorphic, hypomorphic, hypermorphic, antimorphic, and neomorphic made immediate and intuitive sense to me (Muller 1932). I was fascinated by the idea that simple genetic tests could reveal whether a mutation completely or partially inactivated a gene, or changed its function in a more complex manner, without knowing anything about the relevant molecular defects. A similarly appealing concept was that of epistasis, which can tell us how genes work together to control a certain trait—a phenomenon that José's lab used to establish relationships between neurogenic genes in *Drosophila* (my first *GENETICS* paper, de la Concha *et al.* 1988). Gerd Jürgens, with whom I worked extensively while I was a graduate student with Herbert Jäckle at the Max Planck Institute for Developmental Biology, subsequently taught me many of the finer details of Mendelian genetics. I still have fond memories of our collaborative study on how *tailless* and *huckebein* mutations almost completely suppressed a gain-of-function mutation in the maternal-effect gene *torso*, so that the posterior ends of triple mutants very closely mimicked embryos without any *torso* activity—another wonderful example of epistasis (Weigel *et al.* 1990).

As I was drawn to genetics because of the elegance of its methods, it was not so important to me with which organism I would work as a postdoc, be it mice, nematodes, or plants. In the end, *A. thaliana* won out. Alas, the real world of genetics turned out to be a bit more complex than the simple rules I had internalized during my Ph.D. First, I had come to think that amorphic mutations (*i.e.*, null alleles) are always the most informative ones, but this idea was beautifully disproven in one of my favorite papers, from the lab of Gerry Fink

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(GSA Medalist 1982). They showed that a protein null for the *Saccharomyces cerevisiae* MAP kinase Fus3 had a milder phenotype than a kinase-dead point mutant. The reason was that, in the complete absence of Fus3 protein, a related MAP kinase, Kss1, could parachute in and inappropriately moonlight in the Fus3 signaling complex (Madhani *et al.* 1997). Conversely, hypomorphic mutations can be useful to separate different functions of a gene if downstream functions are differentially sensitive to its activity levels. A particularly nice example was the use of different *apetala2* alleles to determine regulatory interactions among floral homeotic genes (Bowman *et al.* 1991), work done by my postdoctoral mentor Elliot Meyerowitz (GSA Medalist 1996) and his lab at Caltech.

A second complication in genetic analyses, I learned, is redundancy. In contrast to *Drosophila*, many plants have undergone multiple rounds of genome duplications during evolution. Even though duplicated genes were often lost again, genetic redundancy appears to be much more of an issue in *A. thaliana* than in *Drosophila*. My first direct contact with genetic redundancy was work in the Meyerowitz lab that showed how the effects of a *CAULIFLOWER* mutation only become apparent when the *APETALA1* (*AP1*) gene is inactivated (Bowman *et al.* 1993); both genes were later found to be recently duplicated paralogs (Kempin *et al.* 1995). In my own postdoctoral work, I came across genetic redundancy between *AP1* and *LEAFY* (*LFY*)—in this case partial functional redundancy, as both genes encode unrelated transcription factors, yet have many overlapping targets (Weigel *et al.* 1992).

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—D.W.

Genetic redundancy was still on my mind when setting up my own lab at the Salk Institute. One outcome of this was the development of a genetic screen based on misexpression and overexpression, where we randomly inserted enhancers derived from a strong viral promoter in the genome (Weigel *et al.* 2000). This approach, activation tagging, took advantage of two special properties of *A. thaliana*: it is easy to transform, so that a single person can generate tens of thousands of transgenic plants in a year or less, and its genome is gene dense, so that random insertions will often be close to genes. We hoped that the mutations would be mostly hypermorphic (increasing normal function), and simply the opposite of loss-of-function mutations, rather than neomorphic (unrelated new function) and misleading. This hope was borne out. We identified, for example, the first plant miRNA mutant, *jaw-d*, and, with it, the only plant miRNA, miR319, that was not first found by random small RNA sequencing (Palatnik *et al.* 2003). In plants, many miRNAs are produced by multiple, highly redundant genes, which is one reason why geneticists had not discovered them before. Gratifyingly, miR319 overexpression in *jaw-d* led to inactivation of all miR319 targets, and the phenotype was, as we had hoped, the opposite of the one seen when the targets are mutated in such a way that they escape miRNA regulation. Activation tagging was also deployed very successfully at the Salk by my colleague Joanne Chory (GSA Medalist 2012), another brilliant geneticist with whom I had the privilege to be associated. Typical for Joanne, she further improved on the original activation tagging and adapted it for suppressor screens.

The success of activation tagging had taught us the value of gain-of-function alleles, which inspired us to take our next cue from Maarten Koornneef. Maarten had pioneered the use of naturally occurring genetic variation to dissect traits important for environmental adaptation (Alonso-Blanco *et al.* 1998). Following Maarten's lead, Joanne and I set out to make use of a worldwide collection of wild *A. thaliana* strains to study first flowering and seedling growth, and later several other adaptive traits. For sure, quantitative genetics was a lot more difficult to learn than Mendelian genetics!

Our main motivation at the time was that nature might have selected more interesting mutations, especially change-of-function mutations (dare I say we were looking for neomorphs?), than the kind of mutations we could easily generate in the lab. While our initial way of thinking about natural alleles was a bit naïve, this new direction paid off handsomely. One discovery of which I am particularly proud is that a special *ACCELERATED CELL DEATH6* (*ACD6*) allele greatly increases the activity of the encoded protein. With this allele, plants are much better protected against a wide range of pathogens. The wrinkle was that the improved pathogen protection comes at the expense of growth—a typical fitness tradeoff (Todesco *et al.* 2010). The special *ACD6* variant is widely found in *A. thaliana* populations, and there are even natural suppressors, that is, some strains have the unusual *ACD6* allele, but do not show the phenotype typically associated with it.

The *ACD6* suppressors provided an example for the kind of epistasis that I had already read about as an undergraduate, with one genetic variant masking the effects of another variant. As I have learned since, quantitative geneticists use a more inclusive definition of epistasis, where any joint effect of two alleles that is different from simple additive action counts as epistasis. Heterosis, or positive epistasis, is perhaps the holy grail of plant genetics, but my own obsession for over a decade has been with negative epistasis, for which we have found many examples in *A. thaliana*. In the cases we study, genes or alleles from different strains interact in the F_1 to inappropriately activate the immune system. The ensuing autoimmunity can greatly compromise growth of the F_1 hybrids, and, in the most extreme instances, be fatal (Bomblies *et al.* 2007). This work brought me back to Muller, who, with Dobzhansky (and sometimes Bateson), is credited for explaining why interspecific hybrids are often highly unfit. While we study F_1 autoimmunity, known as hybrid necrosis,

within a single species—*A. thaliana*—there are also examples of hybrid necrosis in crosses among different plant species, and Coyne and Orr in their textbook on speciation used hybrid necrosis as a classic example of Dobzhansky–Muller type incompatibilities (Coyne and Orr 2004).

As a foundation for the genetic study of natural phenotypic variation, my lab at the Max Planck Institute has invested substantially in genomics, which has culminated in the 1001 Genomes project for this species (The 1001 Genomes Consortium 2016; http://1001genomes.org). In the course of this work, we have become more and more immersed in population and statistical genetics. Similarly, epigenetics has found a way into my lab, although several of our studies in this area have merely reaffirmed the primacy of genetics. I am not sure yet what we will work on in 10 years from now, but I do know that the love of genetics will continue to drive our research program. Even if genetics is not always as simple as I thought as an undergraduate, in the best circumstances, the explanatory power of genetic tests is difficult to beat.

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