Science
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A Map of Local Adaptation in *Arabidopsis thaliana*
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Science **334**, 86 (2011);
DOI: 10.1126/science.1209271

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

and the PHS results and found overlap threefold greater than expected by chance if the two variables were independent. This increased to nearly 10-fold enrichment when we examined overlap among the 10% of climate-related SNPs with the smallest geographic extents; enrichments were strongest for aridity, maximum temperature, precipitation in the driest month, and length of the growing season. Although selection on standing variation also plays a role, these results reveal that selective sweeps are likely an important mode of adaptation in *A. thaliana*. The central role of selective sweeps here suggests that species like *A. thaliana* may reach adaptive limits under rapid climate change, owing to the constraints imposed by waiting for new mutations.

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Acknowledgments: Funded by NIH GM083068 and NSF DEB0519961 to J.B. A.M.H. was supported by a V. Dropkin Postdoctoral Fellowship, and M.W.H. was supported by an NSF Predoctoral Fellowship and a Graduate Assistance in Areas of National Need (GAANN) training grant. F.R. was supported by a Bonus Qualité Reserche (BQR) grant from the University of Lille, and B.B. received funding from a Ph.D. fellowship from the French Research Ministry and a mobility grant from the Collège Doctoral Européen. This is contribution 11-389-J from the Kansas Agricultural Experiment Station. We thank J. Borevitz, A. Fournier-Level, M. Nordborg, A. Platt, J. Schmitt, members of the Bergelson laboratory, and two anonymous reviewers for helpful input. Climate data for the 948 accessions used in these analyses, result files for the correlation analyses, and a browser that allows for viewing the results in their genomic context are available at http://bergelson.uchicago.edu/regmap-data/climate-genome-scan/. The genotype data used for these analyses resulted from the RegMap project (http://regmap.uchicago.edu).

Supporting Online Material

www.sciencemag.org/cgi/content/full/334/6052/83/DC1
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2 June 2011; accepted 25 August 2011
10.1126/science.1209244

A Map of Local Adaptation in *Arabidopsis thaliana*

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Local adaptation is critical for species persistence in the face of rapid environmental change, but its genetic basis is not well understood. Growing the model plant *Arabidopsis thaliana* in field experiments in four sites across the species' native range, we identified candidate loci for local adaptation from a genome-wide association study of lifetime fitness in geographically diverse accessions. Fitness-associated loci exhibited both geographic and climatic signatures of local adaptation. Relative to genomic controls, high-fitness alleles were generally distributed closer to the site where they increased fitness, occupying specific and distinct climate spaces. Independent loci with different molecular functions contributed most strongly to fitness variation in each site. Independent local adaptation by distinct genetic mechanisms may facilitate a flexible evolutionary response to changing environment across a species range.

Adaptation to local environments has been observed experimentally in many organisms (*1*) and may critically limit a given species' capacity to evolve in the face of rapid environmental change (*2*–*4*). However, the molecular basis of local adaptation remains largely unexplored (*5*, *6*). Understanding the genetic mechanisms of adaptation requires understanding the genetic basis of fitness variation within and across natural environments (*7*, *8*). Although genome scans for signatures of past selection have identified candidate loci showing high levels of environmental differentiation (*9*, *10*), few studies have directly connected fitness variation measured in the natural environment of the species to the corresponding molecular variation (*11*, *12*). Determining the extent of local adaptation requires identification of the loci associated with individual fitness in different natural environments, as well as characterization of the distribution pattern of adaptive variants, their environment specificity, and the type of genes involved.

To identify loci associated with fitness in the annual plant *Arabidopsis thaliana*, we grew a geographically diverse set of ecotypes (inbred lines derived from natural populations) across their native range, in replicated common garden experiments in four European field sites (fig. S1). Sites in Oulu (Finland) and Valencia (Spain) spanned the species climate range limits from Nordic to Mediterranean environments; sites in Halle (Germany) and Norwich (UK) represented continental and oceanic climates at similar mid-range latitude (*13*). Mean survival and lifetime fruit (silique) production differed markedly among ecotypes within each planting site, indicating heritable variation among source populations in viability and fecundity (table S1). We carried out a genome-wide association study (GWAS) for survival and silique number using 213,248 single-nucleotide polymorphisms (SNPs) in a mixed-model approach to eliminate confounding due to genomic background (*14*, *15*). For each fitness trait in each of the four field sites, we defined a set of associated SNPs corresponding to the 0.05% of the SNPs that explained the most variance (around 100 per GWAS; figs. S2 and S3). Individual SNPs explained a substantial amount of variation in lifetime fitness, with R^2 in GWAS models ranging on average from 9% for the SNP set associated with survival in England to 24% for the SNP set associated with survival in Finland (fig. S1).

We tested whether alleles associated with high fitness in a given site were more locally abundant than genomic controls, as expected if they contributed to the local adaptation of that population (*16*). Indeed, the geographic centroids of the alleles associated with higher survival in England and Spain and silique number in Germany, England, and Spain were significantly closer to the planting sites in Germany, England, and Spain, respectively, relative to genomic controls; this constitutes evidence of local adaptation for specific loci (Fig. 1). Similar analyses excluding low-frequency polymorphisms provided similar results, demonstrating that the result was not biased as a result of the presence of rare alleles (table S2). In contrast, we found no evidence that the alleles conferring high fitness in Finland were locally abundant. However, our ability to detect

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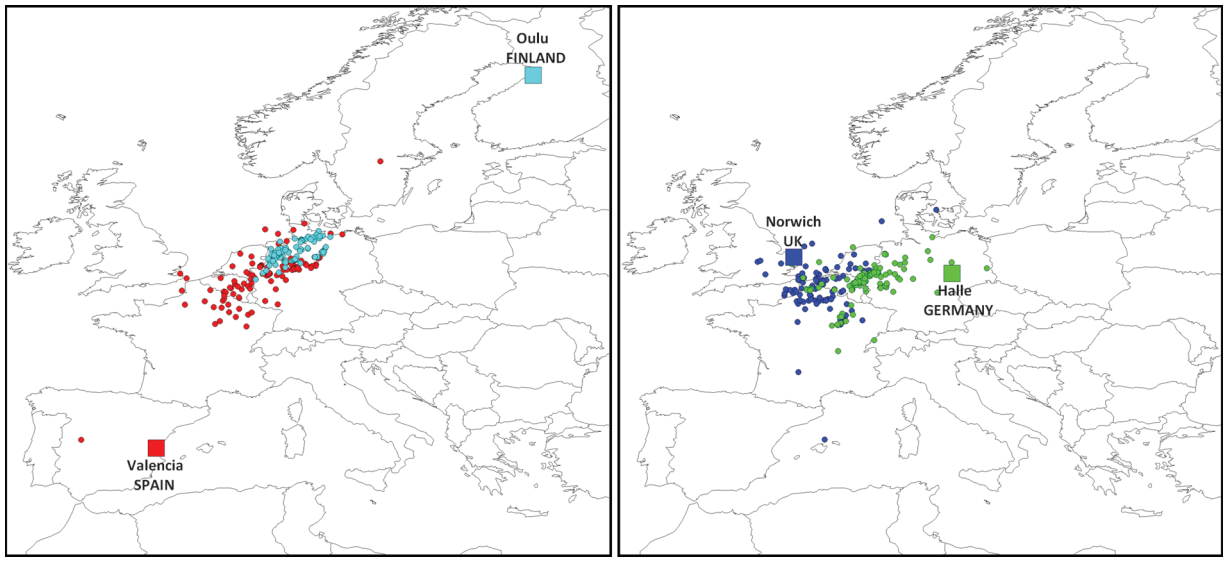

Fig. 1. Locations of the centroids of alleles associated with increased silique number for the 0.05% most strongly associated SNPs in Spain or Finland (**left**) and in England or Germany (**right**). Large squares represent the location of the planting site; small squares represent the centroid of the allele increasing the fitness in the planting site of similar color. The higher-fitness alleles in a particular environment are distributed significantly closer to that location than are genomic controls, as tested by 10,000 random draws.

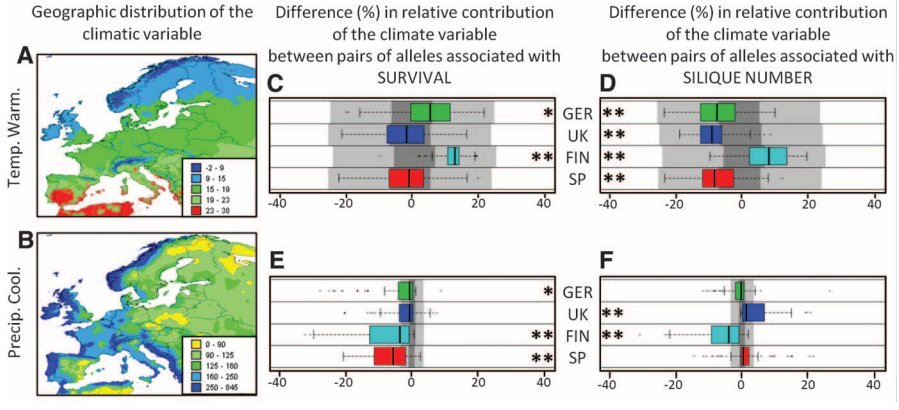

Fig. 2. Influence of temperature and precipitation on the distribution of alleles linked to fitness variation. (**A**) Variation in temperature during the warmest quarter of the year. (**B**) Variation in precipitation during the coolest quarter of the year. (**C** to **F**) Box plots of the difference in climatic contribution between pairs of SNP alleles significantly associated with fitness in Germany, England, Finland, and Spain. Negative values indicate when the deleterious alleles are more correlated with the climate variable; positive values indicate when the beneficial alleles are more correlated with the climate variable. Light and dark shades represent the 25% and 50% quantile statistics of genome-wide neutral expectation obtained through permutation (*16*). $*P < 0.004$, $**P < 0.0001$. All test statistics are reported in table S2.

locally adapted alleles near the species' northern and southern range limits may have been limited by sample size in Finland (*16*) as well as by the sparse sample of local ecotypes available for our sites in Finland and Spain (fig. S1).

We next examined whether local alleles associated with fitness are associated with specific climatic factors, as expected if climate variation has strongly contributed to adaptation. We used maximum entropy models [MaxEnt (*17*)] to infer the contributions of 11 bioclimatic variables to the distribution of each SNP allele (table S3) (*16*) and tested whether fitness-associated alleles occupy specific climate spaces relative to genomic controls. We then used a random resampling procedure to compare climate specificity scores for each fitness-associated SNP for each climate variable to genomic controls. Excluding rare alleles (frequency <5%; table S4) had little effect on the results. The distribution of alleles associated with survival was particularly limited by temperature variables (fig. S4 and table S3). In some cases, the alleles associated with high fitness exhibited greater climate specificity (e.g., temperature of the coolest quarter for survival in Germany, Finland, and Spain; table S4). However, more often alleles associated with low fitness exhibited greater climate specialization (e.g., to precipitation in the coolest quarter for survival and to temperature in the warmest quarter for silique number) (Fig. 2 and table S3). Such alleles may be effectively neutral within the specific climate conditions where they occur, but deleterious when transplanted to field sites with different climates.

We also investigated whether locally adaptive alleles tended to be rare or common relative to the overall genome. If selection favors specific alleles in restricted geographic regions, we expect those variants to be common only in those regions and otherwise rare. On the other hand, if local adaptation acts largely by culling locally deleterious alleles that are neutral elsewhere in the range, then we might expect high-fitness alleles to occur at relatively high frequency. We therefore tested whether the global frequency of the alleles associated with high fitness was different relative to genomic controls. Alleles associated with increased silique number were significantly rarer than genomic controls (table S5), which suggests that their advantage was local for all sites except Finland (where no evidence of local adaptation was found). In contrast, alleles improving survival were high-frequency alleles, which suggests that viability selection keeps deleterious alleles rare, confining their genetic load to environments where they have no effects (i.e., are neutral; fig. S5). We also tested whether fitness-associated SNPs were involved in recent selective sweeps by computing the integrated extended haplotype homozygosity (iEH) around each SNP (*18*, *19*), both in the global sample and in the local population for each field site (*16*). With the exception of survival in Germany and marginally in Finland, we found no evidence that loci associated with fitness had significantly greater iEH than genomic

Table 1. List of candidate genes associated with fitness in field condition.

Chromosome	Position	Site	Climate variable	Trait	Rank	*P*	SNP position	Locus	Gene name	Molecular function (biological process)	Ref.
1	6235221	GER	Temperature seasonality	Silique number	41	3.80×10^{-4}	In the gene	AT1G18140	*LAC1*	Laccase (lignin catabolic process)	(*21*)
							Within 10 kbp	AT1G18130		ATP binding (threonyl-tRNA aminoacylation)	
2	8132698	GER	Precipitation during the warmest quarter of the year	Survival	33	1.08×10^{-4}	In the gene	AT2G18770	*CHR8*	Signal recognition particle binding	(*22*)
							Within 10 kbp	AT2G18780		F-box domain–containing protein	
								AT2G18790	*PHYB*	G protein–coupled photoreceptor (abscisic acid metabolism)	(*25*)
3	5510910	FIN	Precipitation during the coolest quarter of the year	Survival	26	1.12×10^{-4}	In the gene	AT3G16240	*Δ-TIP*	Ammonia transmembrane transporter	
				Silique number	29	4.41×10^{-4}	Within 10 kbp	AT3G16250	*NDF4*	Electron carrier activity (photosystem I)	
								AT3G16260	*TRZ4*	3′-tRNA processing endoribonuclease	
								AT3G16270		(Intracellular protein transport)	
4	1046738	FIN	Isothermality	Survival	4	2.69×10^{-6}	In the gene	AT4G02380	*SAG21*	(Response to water deprivation)	(*23*, *24*)
				Silique number	1	1.11×10^{-4}	Within 10 kbp	AT4G02370			
								AT4G02390	*PARP1*	NAD^+ ADP-ribosyltransferase (protein amino acid ADP-ribosylation)	

controls (table S5), which suggests that no recent selective sweeps have occurred at these loci. Thus, environment-specific fitness may depend more on standing variation than on recent positive selection at specific loci, as recently observed in aspen (*20*).

We examined the genetic architecture of local adaptation by determining whether local selection in different environments more commonly acted upon alternate alleles of the same loci, or if entirely different loci were found among different environments. Individual SNP additive effects for survival were weakly negatively correlated between Finland and England or Spain, which suggests cross-environment tradeoffs at specific loci (fig. S6) (*16*). In contrast, SNP effects on survival were weakly positively correlated between England and Spain, which suggests that they share a similar genetic basis for fitness. However, all the observed correlations across sites were relatively weak, and loci associated with fruit production in England showed little to no effect on fitness in either Finland or Spain; such findings suggest an environment-specific genetic basis. Overall, among the 797 top SNPs, only 12 SNPs were associated with fitness in more than one environment; loci with major genetic effects were largely independent across sites. This result suggests that local adaptation relies on different loci in each environment. Such independent local adaptation by different genetic mechanisms may facilitate flexible evolutionary response to changing environments across the species range.

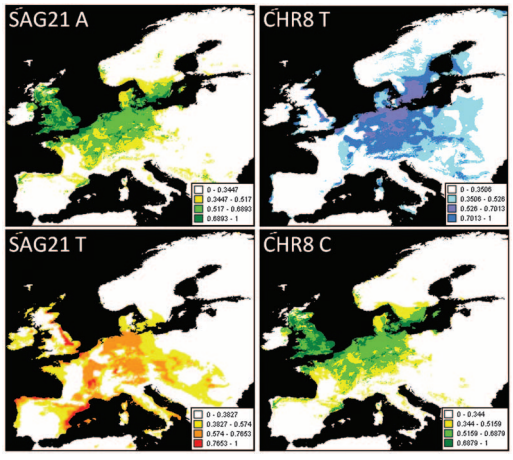

Fig. 3. Geographic distribution probability of the survival-associated alleles located within the *SAG21* gene (**left**) and the *CHR8* gene (**right**). Probabilities were calculated with MaxEnt models as described (*16*). For both genes, the minor allele is distributed at the species range margin following a particular climate space and shows signs of recent positive selection. They correspond to the best candidate genes for local adaptation reported in this study.

We sought insight into the molecular functions of the genes contributing to local adaptation by testing whether the candidate genes present in 10,000–base pair (10-kbp) windows surrounding the associated SNPs were enriched for a particular subset of the Gene Ontology (GO slim) annotations relative to 1000 genomic permutations (*16*). The loci associated with fitness displayed significant enrichment for specific molecular functions in all sites (fig. S7). However, no molecular function was significantly over- or underrepresented in all sets of candidate genes (table S6). Typically, only transcription factor and protein binding activities showed significantly different enrichment for the same trait in more than one site. Protein binding was overrepresented in genes associated with survival in Germany and underrepresented in England, whereas transcription factor activity was underrepresented in both England and Spain. Overall, those molecular functions that were significantly over- or underrepresented relative to the whole genome always differed among field sites. This result suggests that local selection acts not only on different target loci but also on different molecular processes in different environments across the species climate range.

To identify potential candidate genes for local adaptation, we searched for fitness-associated SNPs in the top 0.05% (with minor allele frequency >8% to exclude rare deleterious mutations) that also appeared in the top 0.5% of allele

climate differentiation and in the top 5% of global iEH (Table 1). This screen identified four SNPs within four candidate genes, and linked within 10 kbp to eight additional candidate genes. The three most interesting candidate genes with the associated SNP situated in the coding region were the *LAC1* gene (AT1G18140), involved in the response to necrotrophs (*21*), associated with silique number in Germany; *CHR8* (AT2G18770), involved in DNA repair after viral infection (*22*), associated with survival in Germany; and *SAG21* (AT4G02380), involved in water stress tolerance (*23*, *24*) and associated with survival in Finland. Note that for both *CHR8* and *SAG21*, the allele showing iEH evidence of a selective sweep corresponds to the minor and geographically restricted allele. The *CHR8* allele associated with low survival in Germany is established in the species northern range, and the *SAG21* allele associated with low survival in Finland is restricted to the southern part of the species range (Fig. 3). Recent positive selection may have favored these alleles locally, but their geographic range may be restricted by negative pleiotropic effects on fitness in other environments, such as our field sites.

This study provides robust molecular evidence for broad scale local adaptation in *A. thaliana*. By investigating SNPs linked to loci experiencing real-time selection in different natural environments, we found that the genetic basis of fitness differs dramatically across sites. Moreover, alleles associated with high fitness within sites tend to be local alleles linked to particular climatic factors, providing evidence of local adaptation in *A. thaliana* at the scale of the European continent. Our finding that loci associated with fitness in natural environments display geographic and climatic signatures of adaptation complements recent observations of candidate loci associated with climate (*10*). GWAS of fitness traits measured in multiple natural environments, combined with geographic and climatic analyses, constitutes a powerful approach to identify environment-specific candidate genes for local adaptation.

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Acknowledgments: We thank M. Blázquez, C. Dean, M. Hoffmann, H. Kuittinen, and O. Savolainen for hosting the experiments; J. Anderson, D. Eaton, J. F. Egan, C. Lopez-Gallego, L. J. Martin, C. D. Muir, R. Petipas, J. Roe, and R. N. Schaeffer for managing the field experiments; Brown undergraduates for fruit counts; and J. Bergelson, A. Hancock, and J. Mossman for comments on the manuscript. Supported by NSF grant EF-0425759 and an Alexander von Humboldt Research Award. Supplemental data for the phenotypes and the associated SNPs are available at http://dx.doi.org/10.5061/dryad.37f9t. Genotype data for the SNPs used in this study are available at http://regmap.uchicago.edu.

Supporting Online Material

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2 June 2011; accepted 25 August 2011
10.1126/science.1209271

The Shaping of Modern Human Immune Systems by Multiregional Admixture with Archaic Humans

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Whole genome comparisons identified introgression from archaic to modern humans. Our analysis of highly polymorphic human leukocyte antigen (HLA) class I, vital immune system components subject to strong balancing selection, shows how modern humans acquired the *HLA-B*73* allele in west Asia through admixture with archaic humans called Denisovans, a likely sister group to the Neandertals. Virtual genotyping of Denisovan and Neandertal genomes identified archaic *HLA* haplotypes carrying functionally distinctive alleles that have introgressed into modern Eurasian and Oceanian populations. These alleles, of which several encode unique or strong ligands for natural killer cell receptors, now represent more than half the *HLA* alleles of modern Eurasians and also appear to have been later introduced into Africans. Thus, adaptive introgression of archaic alleles has significantly shaped modern human immune systems.

Whether or not interbreeding occurred between archaic and modern humans has long been debated (*1*, *2*). Recent estimates suggest that Neandertals contributed 1 to 4% to modern Eurasian genomes (*3*), and Denisovans, a likely sister group to the Neandertals, contributed 4 to 6% to modern Melanesian genomes (*4*). These studies, based on statistical genome-wide comparisons, did not address if there was selected introgression of functionally advantageous genes (*5*). We explored whether the highly polymorphic *HLA* class I genes (*HLA-A*, *-B*, and *-C*) (fig. S1) of the human major histocompatibility complex (MHC) are sensitive probes for such admixture. Because of their vital functions in immune defense and reproduction, as ligands for T cell and natural killer (NK) cell re-

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