



Demography and mating system shape the genome-wide impact of purifying selection in *Arabis alpina*

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Plant mating systems have profound effects on levels and structuring of genetic variation and can affect the impact of natural selection. Although theory predicts that intermediate outcrossing rates may allow plants to prevent accumulation of deleterious alleles, few studies have empirically tested this prediction using genomic data. Here, we study the effect of mating system on purifying selection by conducting population-genomic analyses on whole-genome resequencing data from 38 European individuals of the arctic-alpine crucifer *Arabis alpina*. We find that outcrossing and mixed-mating populations maintain genetic diversity at similar levels, whereas highly self-fertilizing Scandinavian *A. alpina* show a strong reduction in genetic diversity, most likely as a result of a postglacial colonization bottleneck. We further find evidence for accumulation of genetic load in highly self-fertilizing populations, whereas the genome-wide impact of purifying selection does not differ greatly between mixed-mating and outcrossing populations. Our results demonstrate that intermediate levels of outcrossing may allow efficient selection against harmful alleles, whereas demographic effects can be important for relaxed purifying selection in highly selfing populations. Thus, mating system and demography shape the impact of purifying selection on genomic variation in *A. alpina*. These results are important for an improved understanding of the evolutionary consequences of mating system variation and the maintenance of mixed-mating strategies.

self-fertilization | demographic history | bottleneck | fitness effects | genetic load

Flowering plants show a great deal of variation in their reproductive modes, and variation in outcrossing rate is particularly common. Although ~50% of flowering plants are predominantly outcrossing, a substantial proportion (35–40%) undergo intermediate levels of outcrossing, whereas only 10–15% are predominantly self-fertilizing (i.e., “selfing”) (1, 2). Whether mixed mating is evolutionarily stable or represents a transitional stage has long been debated (1, 3). Classic population genetic models predict that only high selfing and high outcrossing rates are evolutionarily stable strategies (4). However, mixed mating can be stable in ecologically more realistic models, such as those that account for reduced outcross pollen success with increased selfing (1). Moreover, population genetic models that incorporate linkage indicate that mixed-mating populations may avoid the reduced efficacy of selection associated with high selfing rates (5–7).

Although selfing can be favored because of its genetic transmission advantage and because it can confer reproductive assurance, it also has marked population genetic consequences that might contribute to the long-term demise of highly selfing lineages (6). For instance, highly selfing populations are expected to have a reduced effective population size (N_e) as a result of the direct effect of inbreeding (8, 9). Demographic processes such as frequent extinction and recolonization of local subpopulations (10)

or founder events associated with the shift to selfing (6) can reduce genetic variation in selfers to an even greater extent. Self-fertilization is also expected to lead to elevated linkage disequilibrium, which means that background selection and other forms of linked selection can reduce genetic variation genome-wide, further reducing N_e in selfers (7, 11, 12).

Because the strength of selection scales with N_e (13), natural selection is expected to be less efficient in selfers than in outcrossers. Selfers are therefore expected to accumulate weakly deleterious mutations at a higher rate than outcrossers (14). However, low levels of outcrossing may be sufficient to prevent accumulation of mildly deleterious alleles (15). Furthermore, selfing also increases homozygosity, exposing recessive mutations to selection. This is expected to result in purging of recessive deleterious mutations unless selfing is associated with a strong

Significance

Intermediate outcrossing rates are theoretically predicted to maintain effective selection against harmful alleles, but few studies have empirically tested this prediction with the use of genomic data. We used whole-genome resequencing data from alpine rock-cress to study how genetic variation and purifying selection vary with mating system. We find that populations with intermediate outcrossing rates have similar levels of genetic diversity as outcrossing populations, and that purifying selection against harmful alleles is efficient in mixed-mating populations. In contrast, self-fertilizing populations from Scandinavia have strongly reduced genetic diversity and accumulate harmful mutations, likely as a result of demographic effects of postglacial colonization. Our results suggest that mixed-mating populations can avoid some of the negative evolutionary consequences of high self-fertilization rates.

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reduction in N_e , which renders such purging ineffective (16–18). Theory predicts that purging should also be efficient in mixed-mating populations (17).

Although there is accumulating evidence of relaxed selection on weakly deleterious mutations in highly selfing lineages (5, 19–23), several fundamental questions about the evolutionary genomic consequences of mating systems remain unanswered. Specifically, it is unclear whether partial selfing generally results in purging of recessive deleterious alleles or this effect is possibly overridden by demographic effects, and there are few empirical genome-wide studies that have explicitly examined the selective consequences of mixed mating in plants (but see ref. 24). It is therefore unclear whether mixed-mating plants avoid the negative genetic effects associated with high selfing rates.

The broadly distributed arctic-alpine perennial herb *Arabis alpina* (Brassicaceae) is a promising plant system in which to address the impact of variation in outcrossing rates on genome-wide genetic variation and efficiency of selection. This species harbors populations that express a range of mating strategies from self-incompatible outcrossing (25) through mixed-mating to autonomous selfing (25–28). The colonization history of *A. alpina* has already begun to be characterized (26, 29–31), which facilitates interpretation of global patterns of polymorphism. Finally, the availability of a genome assembly of *A. alpina* (32) greatly facilitates population genomic studies.

In this study, we investigate the effects of mating system and demography on the efficacy of selection in *A. alpina* by population-genomic analyses of whole-genome resequencing data from outcrossing, mixed-mating, and highly selfing populations. We first investigate population structure and test whether populations with higher selfing rates have lower levels of genetic diversity, and then test whether higher selfing rates are associated with relaxed selection against weakly deleterious mutations and purging of strongly deleterious mutations. To do this, we use genome-wide allele frequency distributions at nonsynonymous and synonymous sites to estimate the fraction of weakly deleterious and strongly harmful new nonsynonymous mutations. We further test whether higher rates of selfing are associated with an increase in the frequency of derived alleles with major effects on gene integrity, which would suggest relaxed purifying selection. Finally, we compare two genomic proxies of genetic load, i.e., the reduction in mean fitness of a population caused by deleterious variation (33, 34), among outcrossing, mixed-mating, and highly self-fertilizing populations. Our results are important for an improved understanding of the population genetic consequences of mating system variation.

Results

Sequencing and SNPs. We sampled 38 *A. alpina* individuals from 17 geographical sites, with targeted sampling of two to five individuals from 12 geographical sites harboring self-incompatible outcrossing populations (Greece and Italy), populations with intermediate outcrossing rates (France and Spain), and highly selfing populations (Scandinavia), in addition to a sample of single individuals from five additional geographic locations across the European range of *A. alpina* (SI Appendix, Table S1). Progeny array-based outcrossing estimates have shown that populations from Scandinavia are highly selfing (as much as ~10% outcrossing), whereas intermediate outcrossing rates have been estimated for French and Spanish populations (~19% and ~18%, respectively; SI Appendix, SI Text) (28). We further verified that Greek and Italian individuals produced no offspring after forced self-pollination in the greenhouse. The distribution of genomic runs of homozygosity and decay of linkage disequilibrium supported mating system variation among the populations studied here (SI Appendix, Figs. S1 and S2).

Each individual was resequenced to high coverage (average, 26 \times ; range, 16–45 \times) by using Illumina short-read technology. We

called SNPs and applied stringent filtering criteria to identify a total of 1,514,615 high-quality SNPs, of which 98,564 were 0-fold degenerate nonsynonymous (i.e., sites at which any mutation will result in a nonsynonymous change), with a mean nucleotide diversity (π) of 0.0027, and 65,821 were fourfold degenerate synonymous (i.e., synonymous sites at which any mutation will result in a synonymous change), with a mean nucleotide diversity of 0.0102 (SI Appendix, Table S2).

Population Structure Has a Strong Geographic Component. We analyzed population structure with two model-based Bayesian clustering approaches, implemented in the software fastSTRUCTURE (35) and TESS3 (36), based on 25,505 fourfold synonymous SNPs (Methods). Both methods, as well as principal component analysis (PCA), gave very similar results, and supported the presence of five clusters (Fig. 1) that were substantially differentiated (average pairwise fixation index, F_{ST} , 0.56; range, 0.39–0.82; SI Appendix, Table S3), in good agreement with previous analyses of population structure in *A. alpina* (30). These clusters correspond to a central European population of mixed-mating individuals from France, Germany, Poland, and Switzerland; a northern European population of highly self-fertilizing individuals from Sweden, Norway, and Iceland; a mixed-mating population containing individuals from Spain and Madeira; and two outcrossing populations representing individuals from Italy and Greece, respectively (Fig. 1). Subsequent population-genetic analyses are presented separately for regional population samples from each of these geographical regions.

Genetic Diversity Is Maintained in Mixed-Mating but Not in Highly Selfing Populations. For each regional population, we quantified nucleotide diversity at three categories of sites—synonymous sites, nonsynonymous sites, and intergenic sites—in regions of low gene density and high recombination rate (Table 1 and SI Appendix, Table S4). At all three categories of sites, levels of nucleotide diversity (π) varied by an order of magnitude or more

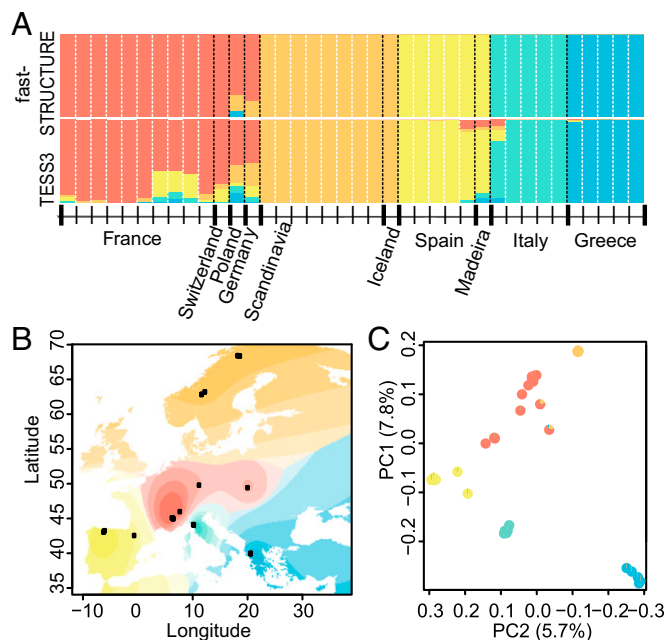


Fig. 1. Bayesian clustering analysis supports a strong geographic component to population structure in European *A. alpina*. (A) Ancestry proportions for $K = 5$ clusters correspond closely to geographical sampling locations. (B) Geographic interpolation of genetic structure across Europe based on TESS3 results for $K = 5$. (C) PCA of genetic data, with pie charts showing ancestry proportions for $K = 5$ and colors indicating geographic origin.

among regional populations (Table 1 and *SI Appendix, Table S4*). The outcrossing Greek population was the most genetically diverse (synonymous diversity π_S , 0.008), whereas the highly self-fertilizing Scandinavian populations had very low nucleotide diversity (π_S , 0.0002; Table 1). Levels of nucleotide diversity were intermediate and of a similar magnitude in outcrossing Italian and mixed-mating French and Spanish populations (Table 1), which also have similar demographic histories (*SI Appendix, Fig. S7*). These results thus suggest that, in *A. alpina*, mixed-mating populations maintain similar levels of genetic diversity as outcrossing populations. Similar patterns were seen for nonsynonymous sites, although the relative reduction in diversity in Scandinavia was less severe for nonsynonymous than for synonymous sites (*SI Appendix, Table S4*). This resulted in a markedly elevated ratio of nonsynonymous to synonymous nucleotide diversity (π_N/π_S) in Scandinavia (Table 1).

Selfing, but Not Mixed Mating, Is Associated with a Genomic Signature of Relaxed Purifying Selection. To test whether the impact of purifying selection varied with mating system, we estimated the distribution of negative fitness effects (DFE) of new nonsynonymous mutations using the software DFE- α (37) (further details provided in *Methods*). This method can detect changes in selection in association with plant mating system shifts, including purging of strongly deleterious mutations, which should be visible as an increase in the proportion of new mutations under strong purifying selection (38), and corrects for effects of demographic changes on allele frequency spectra by using a simple population size change model. We summarized the strength of purifying selection, defined as the product of the effective population size N_e and the selection coefficient s , in three bins, ranging from nearly neutral to strongly deleterious ($0 < N_e s < 1$; $1 < N_e s < 10$; $N_e s > 10$). Although the DFE of the mixed-mating Spanish and outcrossing Greek populations differed, there were no significant differences between the DFE of the outcrossing Italian population and the mixed-mating Spanish and French populations (Fig. 2A). The inferred proportion of strongly deleterious new nonsynonymous mutations was not generally higher in the mixed-mating French and Spanish populations than in the outcrossing Greek and Italian populations (Fig. 2A). Thus, *A. alpina* populations undergoing as much as 80% selfing do not show population-genomic evidence of relaxed purifying selection or increased purging of recessive deleterious mutations.

In contrast to results for mixed-mating populations, several lines of evidence suggest that selection against deleterious alleles is compromised in highly self-fertilizing Scandinavian *A. alpina*. First, there was a strong difference in the DFE of nonsynonymous mutations, with a strong, significant reduction in selection against strongly deleterious nonsynonymous mutations (i.e., $N_e s > 10$) in Scandinavia compared with all other regional populations (Fig. 2A). Thus, DFE analyses suggest that the Scandinavian population could be accumulating strongly deleterious nonsynonymous mutations.

In line with our inference of accumulation of deleterious alleles in Scandinavian *A. alpina*, we found that derived alleles with a major effect on gene integrity (*Methods*) were at a markedly higher frequency relative to derived synonymous alleles in Scandinavia compared with all other regional populations (Fig. 2B). Because selected and neutral allele frequency spectra can be differently affected by demographic changes even in the absence of an actual change in selection (39–41), we considered additional proxies for genetic load. First, we estimated the average number of homozygous derived major-effect genotypes (Fig. 2C), which is expected to be proportional to genetic load if deleterious mutations act recessively, and then we estimated the average number of derived major-effect alleles (Fig. 2D), which is proportional to genetic load if deleterious mutations have additive effects (42). According to both statistics, the highly selfing Scandinavian regional population had an elevated genetic load compared with

Table 1. Population genetic summary statistics for regional populations

Populations (n)	S_5^*	π_S^\dagger	π_N/π_S^\ddagger
Greece (5)	30,920	0.0080	0.2740
Italy (5)	17,971	0.0054	0.2820
Spain (5)	15,852	0.0046	0.2911
France (10)	19,661	0.0052	0.2764
Scandinavia (8)	589	0.0002	0.3936

*Segregating fourfold synonymous SNPs.

†Mean fourfold synonymous nucleotide diversity.

‡Mean 0-fold degenerate nonsynonymous/fourfold degenerate synonymous polymorphism.

mixed-mating populations, and outcrossing and mixed-mating populations were not different from each other (Fig. 2C and D). Estimates of additive load were lower in mixed-mating than in outcrossing populations, but the difference was not statistically significant (Fig. 2D). In addition, the number of fixed derived major-effect variants in Scandinavia was highly inflated (~70% increase) compared with the outcrossing and mixed-mating populations (*SI Appendix, Table S5*). A similar pattern was seen for derived nonsynonymous variants as well as derived nonsynonymous variants at evolutionarily constrained sites, and when considering each geographical population separately (*SI Appendix, Figs. S3 and S4 and Table S5*). Overall, this suggests that the highly selfing *A. alpina* from Scandinavia are accumulating deleterious mutations, whereas we observe no statistically significant evidence of purging of genetic load in mixed-mating populations.

A Recent Bottleneck and Selfing Explain Polymorphism in the Scandinavian Population. Theory predicts that high levels of self-fertilization should result in effective purging of recessive deleterious variation unless selfing is associated with strong reductions in N_e (17). Given that we observed no evidence for purging and a strong reduction in genetic variation in Scandinavian *A. alpina*, we asked whether this could have resulted from a bottleneck, or if increased background selection caused by selfing is sufficient to explain the reduction of diversity.

Previous phylogeographic analyses have shown that *A. alpina* likely originated in Asia Minor and subsequently spread westward approximately 500 kya (29, 31). Population-genetic analyses have identified Central European populations as the most likely source for Scandinavian *A. alpina* populations (30), but no explicit demographic model has yet been fit to estimate the timing or demographics of colonization of Scandinavia by *A. alpina*. For this purpose, we used a maximum likelihood-based approach to estimate the parameters of a demographic model of colonization of Scandinavia by using a 2D site frequency spectrum (2D-SFS; *SI Appendix, Fig. S5*) based on a scattered sample of individuals from Central Europe and the highly selfing Scandinavian *A. alpina* (*Methods*). For analyses of demographic history, we used a set of 12,967 SNPs in intergenic regions with low gene density and high recombination rate, which are expected to be less affected by linked selection and thus useful for demographic inference (12, 43). According to our best-fit model, the split between Central Europe and Scandinavia occurred ~20 kya and was associated with a prolonged bottleneck (Fig. 3A and *SI Appendix, Figs. S6 and S7 and Table S6*).

We conducted population-genetic simulations to assess whether the reduction in diversity in Scandinavia could be explained by a stronger impact of background selection caused by selfing, without additional demographic changes. These simulations, which used realistic settings for *A. alpina* genome structure, including variation in recombination rate, gene density, and mutation rates, and a realistic distribution of negative fitness effects (*Methods*), show that models that incorporate a transition to selfing but no demographic

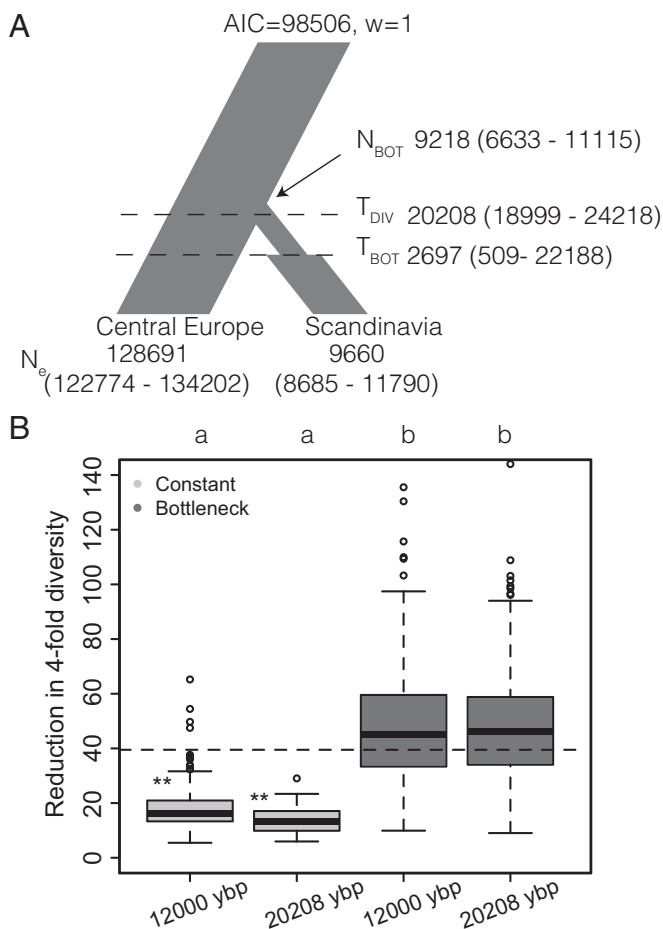


Fig. 3. A recent bottleneck and selfing explain the reduction of polymorphism in Scandinavia. (A) The best-fit demographic model of the colonization of Scandinavia from a Central European population. Estimated times are given in years before present (ybp). (B) Background selection alone does not explain the reduction in diversity in Scandinavian *A. alpina*. Boxplots show the ratio of synonymous polymorphism between an outcrossing population and a 90% selfing population experiencing a constant population size or a 10-fold bottleneck, with the two populations diverging 12,000 ybp or 20,208 ybp. The dashed line indicates the observed ratio of synonymous polymorphism in Central Europe to that in Scandinavia. Letters indicate significant difference between models (Mann–Whitney test, $P < 0.001$). Asterisks indicate an observed neutral diversity reduction significantly greater than that expected based on 300 simulations.

In contrast to the lack of differences in purifying selection between outcrossing and mixed-mating populations, we found strong evidence for accumulation of deleterious mutations in highly self-fertilizing Scandinavian *A. alpina*. Indeed, our DFE analyses indicate less efficient selection against strongly deleterious alleles, and we observe an increase in the relative allele frequency and fixed derived major-effect mutations, as well as elevated additive and expressed genetic load in Scandinavian *A. alpina*. These results suggest that deleterious alleles are not efficiently selected against and have been able to increase in frequency in these populations. In the context of human population history, theory and simulations have shown that range expansions (45) or strong and extended bottlenecks (39, 41, 42) can lead to increased genetic load. It has previously been shown that genetic variation is strongly reduced over a vast geographical area representing the northern part of the distribution of *A. alpina* (30). Our demographic inference and population-genetic simulations suggest that this reduction of genetic variation is most likely a result of postglacial colonization bottlenecks. Thus, bottlenecks associated

with range expansion appear to have strongly reduced N_e and increased the impact of drift in the Northern part of the species range, causing accumulation of deleterious variants in Scandinavian *A. alpina*. The impact of demographic history on genetic load is currently a strongly debated topic in human population genetics, in which studies on the effect of the out-of-Africa bottleneck on genetic load have come to different conclusions depending on the statistics they applied (39, 46–48). Here, we extend these studies to a plant species and document increased accumulation of deleterious mutations in bottlenecked Scandinavian *A. alpina*.

Increased background selection can lead to sharply reduced genetic diversity in highly selfing populations (7, 12), but our forward population genetic simulations show that this effect alone cannot explain the reduction in diversity in Scandinavia, whereas a model with selfing and a population size reduction is consistent with the observed reduction in diversity. At present, however, we cannot rule out a contribution of positive selection, or other changes in selection during range expansion, to reduced diversity in the Scandinavian *A. alpina* population. Indeed, reciprocal transplant experiments have documented adaptive differentiation between Spanish and Scandinavian populations of *A. alpina* (49). Although elevated load can be associated with enhanced local adaptation following a range expansion (50), this raises the possibility that some of the increase in frequencies of major-effect variants in Scandinavia may have been directly or indirectly driven by positive selection. However, we believe it is unlikely to result in the genome-wide signature of relaxed purifying selection that we observe in Scandinavian *A. alpina*. Empirical identification of genomic regions responsible for local adaptation and population genomic studies using larger sample sizes will be needed to explore the genomic impact of positive selection.

Here, we have investigated the impact of demographic history and mating system on genomic patterns of variation in *A. alpina*. Our results show that mixed-mating populations maintain genetic variation and purifying selection at similar levels as outcrossing populations. In contrast, we find an increase in genetic load of demographic effects associated with postglacial range expansion. Our results are important for a more general understanding of the impact of mating system and demographic history on genomic variation and selection in plants.

Methods

Data and Sequencing. We performed paired-end (100-bp) whole-genome resequencing of 38 *A. alpina* individuals from Europe (SI Appendix, Table S1) by using libraries with an insert size of 300–400 bp (SI Appendix, SI Text) on an Illumina HiSeq 2000 instrument (Illumina). We obtained a total of 10,079 Gbp (quality score QC > 30) with a mean coverage of 26x, ranging from 16x to 45x.

Quality Assessment, Trimming, Genotype Calling, and Filtering. Adapter-trimmed reads were mapped to the *A. alpina* V4 reference genome assembly (32) by using BWA-MEM v0.7.8 (51), and duplicate-free BAM alignment files were further processed by using the Genome Analysis Toolkit (52) (v.3.4.0; SI Appendix, SI Text). The *A. alpina* genome assembly is enriched for repetitive elements relative to Brassicaceae relatives (32), so we employed a variety of hard and custom filtering techniques (SI Appendix, SI Text) to avoid calling SNPs in regions of the genome that putatively represent copy number variants. After applying all filters, the dataset contained 1,514,615 SNPs and 43,209,020 invariant sites.

Inference of Population Structure and Population-Genetic Analyses of Selection. Population structure was inferred by using a combination of PCA and Bayesian clustering analysis with the use of fastSTRUCTURE v1.0 (35) and TESS v3 (36) (SI Appendix, SI Text).

For each of the five regional populations identified, we estimated summary statistics (S , π , Tajima's D) at fourfold degenerate synonymous sites, 0-fold degenerate nonsynonymous sites, and intergenic sites in regions with high recombination and low gene density (Table 1 and SI Appendix, SI Text). We estimated the DFE by using DFE- α v2.15 (37) on folded fourfold and 0-fold SFS under a stepwise population size change model (SI Appendix, SI Text and Table S7). We compared the DFE of regional populations based on 200 bootstrap replicates.

Major Effect Mutations and Genetic Load. Presence and frequency of major effect mutations, i.e., loss of start and stop codons, gain of stop codons, and changes in splice sites, were calculated per population by using snpEFF v4.2 (53). To avoid reference biases, we polarized the SNPs using the *Arabidopsis thaliana* genome assembly (ASM14841v1) (54) as an outgroup (SI Appendix, SI Text). As a proxy for genetic load, we estimated the average number of derived nonsynonymous and major-effect homozygous genotypes per individual (41, 46), and the average number of derived alleles for nonsynonymous and major-effect alleles per individual (42) for each regional population. We repeated these analyses for nonsynonymous variants at highly constrained sites (SI Appendix, SI Text). In addition, we counted the total number of fixed derived nonsynonymous and major-effect alleles for each regional population.

Demographic Modeling and Simulations. We conducted demographic inference in the software fastsimcoal2 v2.5.2.21 (55). To estimate parameters associated with the origin of Scandinavian *A. alpina*, we compared three demographic

models (SI Appendix, Fig. S5) using 2D joint SFS based on a scattered sample from central Europe and the Scandinavian population (SI Appendix, SI Text and Fig. S6). We used 12,967 intergenic sites, a mutation rate of 7×10^{-9} , and a generation time of 1.5 y. We used forward simulation in SLiM2 v2.1 (56) to assess the impact of demography and selection associated with a shift to selfing on genetic diversity in the Scandinavian population under four demographic models with varying bottleneck severity and population split time (SI Appendix, SI Text).

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