CLIMATE ADAPTATION

The evolution of white-tailed jackrabbit camouflage in response to past and future seasonal climates

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The genetic basis of adaptive traits has rarely been used to predict future vulnerability of populations to climate change. We show that light versus dark seasonal pelage in white-tailed jackrabbits (*Lepus townsendii*) tracks snow cover and is primarily determined by genetic variation at endothelin receptor type B (*EDNRB*), corin serine peptidase (*CORIN*), and agouti signaling protein (*ASIP*). Winter color variation was associated with deeply divergent alleles at these genes, reflecting selection on both ancestral and introgressed variation. Forecasted reductions in snow cover are likely to induce widespread camouflage mismatch. However, simulated populations with variation for darker winter pelage are predicted to adapt rapidly, providing a trait-based genetic framework to facilitate evolutionary rescue. These discoveries demonstrate how the genetic basis of climate change adaptation can inform conservation.

Preservation of genetic diversity is a primary goal of conservation biology (*1*), reflecting the critical role that genetic variation plays in promoting rapid adaptation to environmental change (*2*, *3*). Although there has been progress in dissecting the genetic basis of adaptation in some species (*4*–*6*), rarely has such information been used to guide the conservation of populations (*7*, *8*). These shortcomings reflect the difficulties of genetic mapping in natural populations (*9*) and using genotype-to-phenotype maps to facilitate adaptive responses (*7*).

Circannual shifts in morphology, physiology, and behavior cued by changes in photoperiod allow many species to buffer the challenges of seasonal environments (*10*). Seasonal molts to winter-white pelage and plumage have evolved in at least five animal families to maintain crypsis in snow-covered environments (*11*). Winter coloration has been directly tied to survival in snowshoe hares (*12*, *13*), and several species appear vulnerable to camouflage mismatch caused by global snow cover declines (*14*–*18*). We examined how snow cover variation has shaped the evolution and future adaptive potential of winter camouflage in white-tailed jackrabbits (*Lepus townsendii*), a North American species undergoing widespread population declines (*19*).

Winter coat color tracks variation in snow cover across the white-tailed jackrabbit range

Winter coat color varies from brown to white across the white-tailed jackrabbit distribution (*11*, *20*). We used 1312 georeferenced records to estimate a species distribution model (Fig. 1 and figs. S1 and S2A) (*21*) and used climate covariates and 196 museum specimens with mostly white or brown pelage to build a probabilistic model of winter coloration across the range (Fig. 1A and tables S1 and S2).

Consistent with previous work (*11*), the probability of an animal having white pelage increased with snow cover duration and a relate of snow seasonality (mean diurnal temperature range) and decreased with an index of snow transience (isothermality; table S1). Our model predicted a mosaic of winter-white or -brown populations separated by zones of intermediate coat color probabilities. We found a steep winter color gradient between the Rocky Mountains and the Great Plains of Colorado (Fig. 1C), which included a previously described population with continuous coat color variation (*20*).

The genetic basis of winter coat color

To dissect the genetic basis of winter color variation, we sequenced (62.5×; table S3 and data S1 and S2) and assembled a white-tailed jackrabbit genome (48.03 Mb scaffold N50; table S3). We also sequenced 74 genomes from the coat color polymorphic zone in Colorado (Fig. 1C) to low coverage (~1.8×; table S4), of which seven genomes were also resequenced to moderate coverage (~12.2×; data S1 and table S5). Analysis of 239,834 unlinked single nucleotide polymorphisms (SNPs) showed weak population structure partitioned across two genetic clusters not broadly coincident with coat color variation (fig. S3E; between-cluster weighted fixation index, F_{ST} = 0.036). Spectrophotometric analysis of six dorsal regions (fig. S4) uncovered considerable variation in dorsal brightness, hue, and contrast (n = 61 specimens, 51% variance in the first principal component (PC1) figs. S4 and S5, A and D); variegation (14.6% variance in PC2; figs. S4 and S5, B and E); and mottling (7.5% variance in PC3; figs. S4 and S5, C and F).

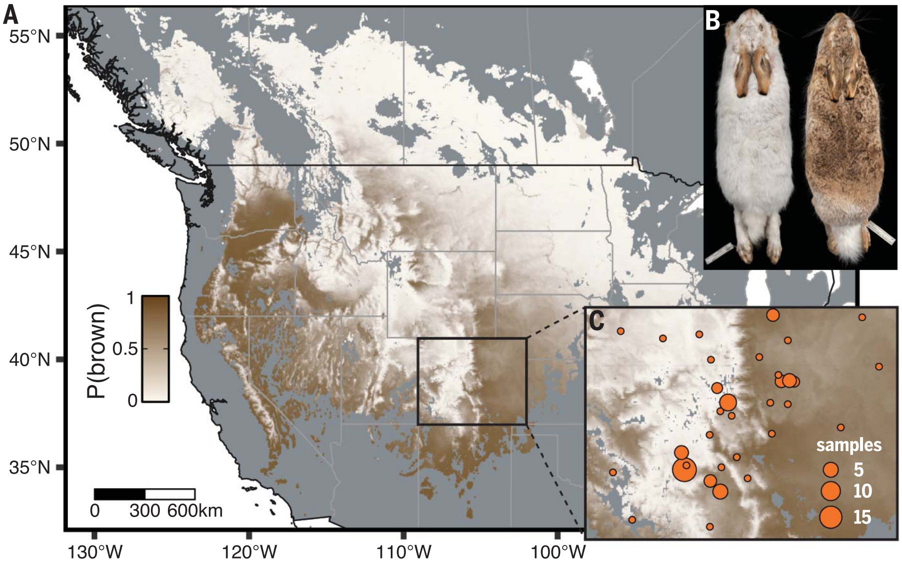

Fig. 1. Winter coat color variation in white-tailed jackrabbits. (**A**) Probability of winter-brown coats across the modeled white-tailed jackrabbit distribution. (**B**) Representative winter coat color variation [Photo credit: IV.ZM.4312.P @ Denver Museum of Nature & Science]. (**C**) Sampling locations used for association mapping across Colorado, scaled by sample size.

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White versus brown categories used in our binary phenotypic model (Fig. 1) consistently partitioned continuous color variation along PC1 (fig. S4B). Genome-wide association tests between 5,557,716 SNPs and PC1 of the spectrophotometric data revealed significant associations robust to population structure on two scaffolds, each containing one gene involved in melanogenesis (Fig. 2 and fig. S6).

One association centered on corin serine peptidase (*CORIN*; Fig. 2B; $P = 7.26 \times 10^{-16}$), a serine peptidase expressed in hair follicles that acts as a downstream suppressor of the agouti signaling protein (*ASIP*) (*22*). Loss-of-function mutations in *CORIN* have been associated with enlarged pheomelanin bands and lighter pelage in tigers (*23*) and mice (*24*). The other association centered on the endothelin receptor type B (*EDNRB*, Fig. 2D; $P = 3.31 \times 10^{-22}$), a G protein-coupled receptor essential to developmental migration and differentiation of melanocyte precursors (*25*, *26*). *EDNRB* mutations cause white piebald spotting due to absence of melanocytes (*27*). For both genes, top associated variants were noncoding, consistent with a regulatory basis of seasonal camouflage variation.

We also performed association tests on all 74 jackrabbits, binning color as white or brown, and found two additional associations. One overlapped a noncoding region ($P = 1.29 \times 10^{-14}$; figs. S6B and S7) near genes from the α2-macroglobulin gene family, which have been linked to reproduction (*28*–*30*), and may reflect a correlated seasonal trait. The other overlapped *ASIP* ($P = 1.38 \times 10^{-14}$; fig. S6B), a well-known signaling protein that shifts melanogenesis to lighter phaeomelanin production or inhibits pigment production (*31*). *ASIP* has been associated with discrete winter coat color polymorphisms in snowshoe and mountain hares (*6*, *32*).

We next used mass spectrometry to generate high-confidence genotypes for 59 jackrabbits with spectrophotometric data at 34 linked SNPs (average within-gene $r^2 \geq 0.93$) across *CORIN* ($n = 13$ SNPs), *EDNRB* ($n = 9$ SNPs), and *ASIP* ($n = 12$ SNPs) (fig. S8 and data S1 and S3). *CORIN* ($P = 6.82 \times 10^{-9}$) and *EDNRB* ($P = 7.73 \times 10^{-12}$) alleles remained strongly associated with PC1 (tables S6 and S7), showing largely additive (Fig. 2, C and E; all $P > 0.05$, dominance deviation test; tables S8 and S9) and independent effects ($P > 0.05$; Fig. 2F, fig. S9, and table S10). *ASIP* was not associated when including the other genes as covariates (tables S6 and S7), but we detected epistatic interactions between the top associated SNPs at *ASIP* and *CORIN* ($P < 0.05$; table S10), consistent with known molecular interactions between these genes (*22*). A linear model of the top associated SNPs from each gene explained 65% of phenotypic variation (model D, table S11). Although a precise estimate of effect sizes awaits more sampling, winter camouflage in white-tailed jackrabbits appears to be primarily determined by large-effect additive genetic variation at *CORIN* and *EDNRB*, with a minor contribution of *ASIP*.

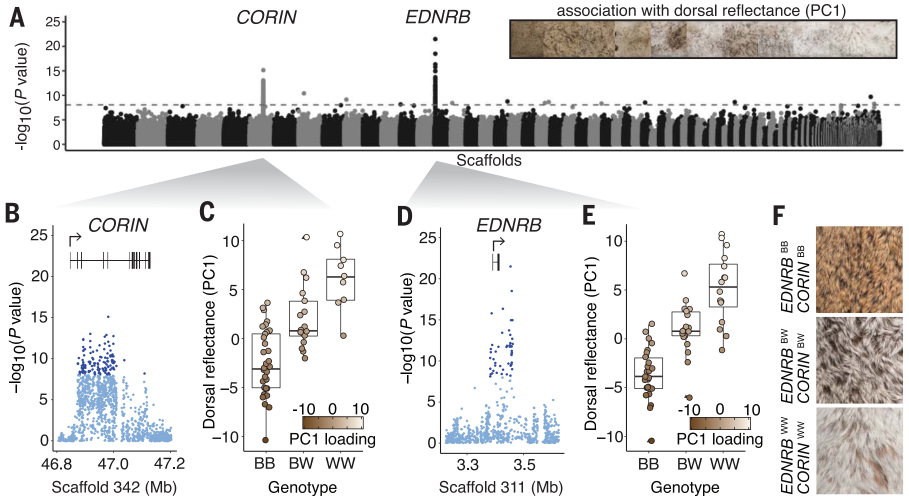

Fig. 2. The genetic basis of winter coat color variation. (**A**) Genome-wide associations ($-\log_{10}P$ values; 5,557,716 SNPs) with winter coat color (inset: dorsal photos ordered by PC1) of 61 jackrabbits (dashed line, Bonferroni-corrected $P = 0.05$). (**B** to **E**) Local associations, gene structures, and dorsal reflectance across assayed diploid genotypes (BB, homozygous brown; BW, heterozygous; WW, homozygous white) for *CORIN* (B and C) and *EDNRB* (D and E). Significant associations are highlighted in dark blue (Bonferroni-corrected $P \leq 0.05$). (**F**) Dorsal images of specimens with double homozygous or heterozygous *CORIN* and *EDNRB* genotypes [Photo credit: IV.ZM.4312.P @ Denver Museum of Nature & Science].

Multigenic winter camouflage adaptation is shaped by selection on ancient genetic polymorphisms and gene flow between species

Genome-wide comparisons among white-tailed jackrabbit genomes revealed increased scaled absolute genetic divergence between winter-white and winter-brown associated alleles of *CORIN*, *EDNRB*, and *ASIP* (Z-score ≥ 3; Fig. 3A and fig. S10), indicating that seasonal camouflage variation did not arise from recent mutations in white-tailed jackrabbits. To examine the history of these genes, we combined white-tailed jackrabbit genomes with 10 new and 19 previously published (*6*, *32*–*36*) genomes (~7.5 to 33.5×; table S5) from nine other *Lepus* species, including four showing seasonal camouflage (data S1). Genome-wide analysis clustered white-tailed jackrabbits with three other color-changing species (Fig. 3B, fig. S11, and table S12). *CORIN*, *EDNRB*, and *ASIP* showed discordant local genealogies whereby winter-brown alleles from white-tailed jackrabbits grouped with black-tailed jackrabbits, a winter-brown species, whereas winter-white alleles grouped with closely related winter-white species (Fig. 3B and fig. S12). The estimated divergence time between the white and brown haplotypes exceeded 3 million years (Myr) at all three genes [*EDNRB* = 4.2 Myr (95% highest posterior density (HPD) 3.3 to 5.0 Myr); *CORIN* = 3.3 Myr (95% HPD 2.9 to 4.3 Myr); *ASIP* = 3.1 Myr (95% HPD 2.4 to 3.7 Myr); fig. S13], suggesting a common ancestor near the onset of *Lepus* diversification (*37*).

Deep phylogenetic discordance at each gene could reflect gene flow from another species (*38*). Consistent with this, divergence (d_{xy}) across an ~88-kb interval overlapping *ASIP* was reduced between black-tailed jackrabbits and the white-tailed jackrabbit brown allele relative to simulated expectations (Fig. 3C; fig. S14, B and C; and table S13). By contrast, the white allele showed normal levels of divergence compared to other winter-white hares (Fig. 3D and fig. S14D). Black- and white-tailed jackrabbits occupy similar prairie habitats with overlapping ranges and show substantial genome-wide introgression (D-statistic = 0.19, $P << 0.0001$; 4% admixture (f_G), $P << 0.0001$). The persistence of introgressed alleles, a binary association (fig. S6B), and a central role in color evolution (*31*) suggest that *ASIP* contributes to a component of color variation not captured by our measurements. This is the third instance of introgression at *ASIP* contributing to winter camouflage in hares (Fig. 3B) (*6*, *32*), suggesting that some genes may be evolutionary hotspots for adaptive introgression (*39*).

The evolutionary processes shaping variation at *CORIN* and *EDNRB* were less clear. Divergence (d_{xy}) between black-tailed jackrabbits and the brown-associated intervals of both genes were not unusually shallow (Fig. 3C), as expected with recent introgression. However, closer inspection revealed local phylogenetic variation that is consistent with ancient gene flow (fig. S14). Although the causative mutations remain unknown, the top associated

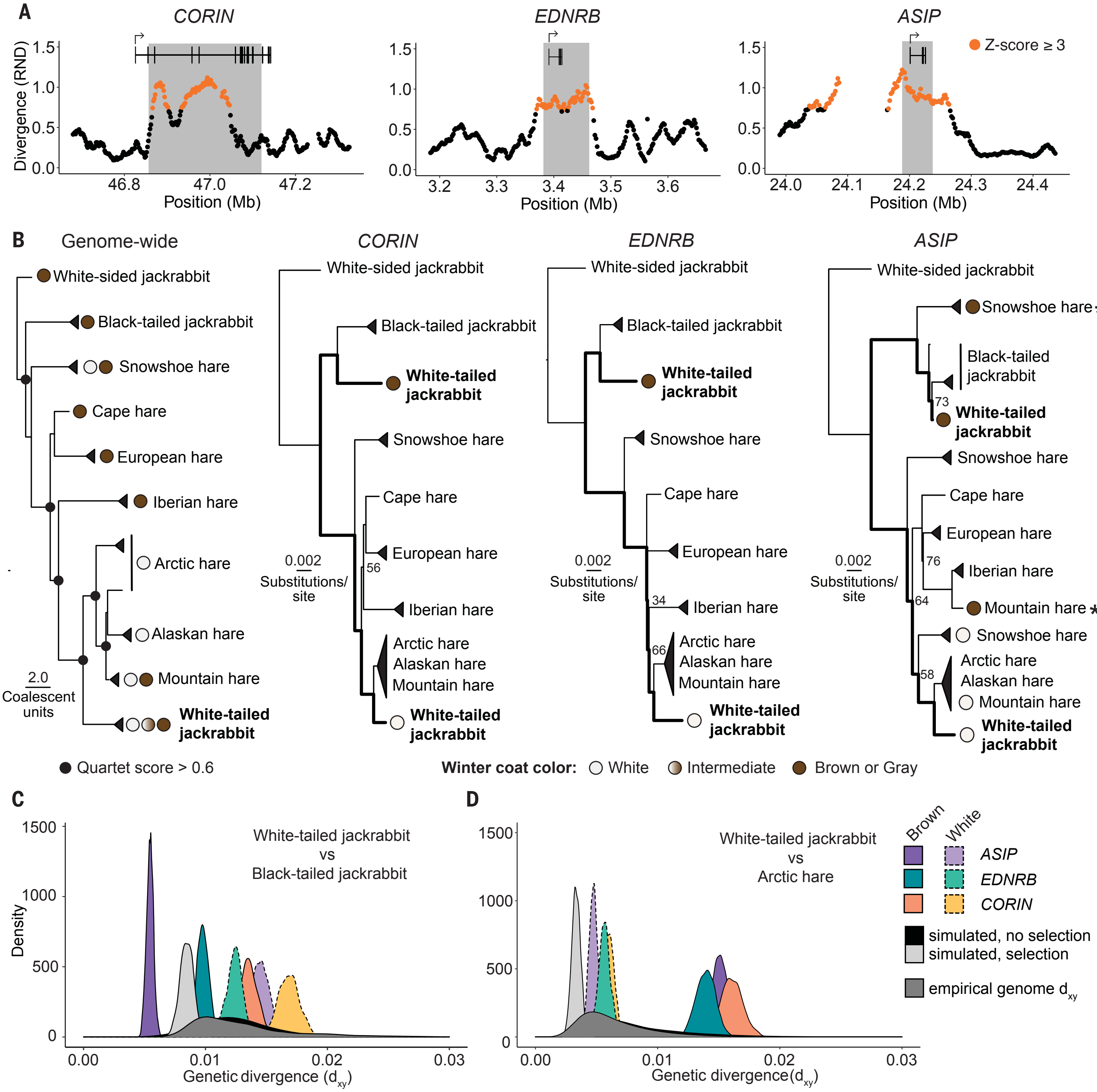

Fig. 3. Evolution of winter coat color variation. (**A**) Scaled absolute genetic divergence (RND) in 20-kb sliding windows (dots, 2-kb step size) between one homozygous winter-white and winter-brown genome. Association intervals are gray, orange dots are windows of elevated divergence (RND Z-score ≥ 3), and gaps represent missing data in the reference assembly. (**B**) Phylogenies of *CORIN*, *EDNRB*, and *ASIP* (associated intervals) differed from the multispecies coalescent tree (43,430 50-kb windows, fig. S11). An asterisk denotes species for which winter pelage variation has previously been associated with introgression (*6*, *33*). Branches with bootstrap support <80 are labeled. (**C** and **D**) Empirical and simulated distributions of genetic divergence (d_{xy}) genome-wide and for *CORIN*, *EDNRB*, and *ASIP* between white-tailed jackrabbits and (C) black-tailed jackrabbits or (D) Arctic hares.

SNPs at both genes fell outside putative introgression tracts. These patterns suggest a history of recombination among ancient color alleles at *CORIN* and *EDNRB*, likely maintained by long-term spatially varying selection (*40*). Collectively, these findings indicate that multigenic winter camouflage adaptation (Fig. 1), shaped by selection on standing and introgressed variation (Fig. 3), has long been important to white-tailed jackrabbit survival.

Future climate change vulnerability and adaptive potential of seasonal camouflage variation

Seasonal snow cover is predicted to decline over the next century (*41*), which may reduce the adaptive value of winter-white coats (*11*).

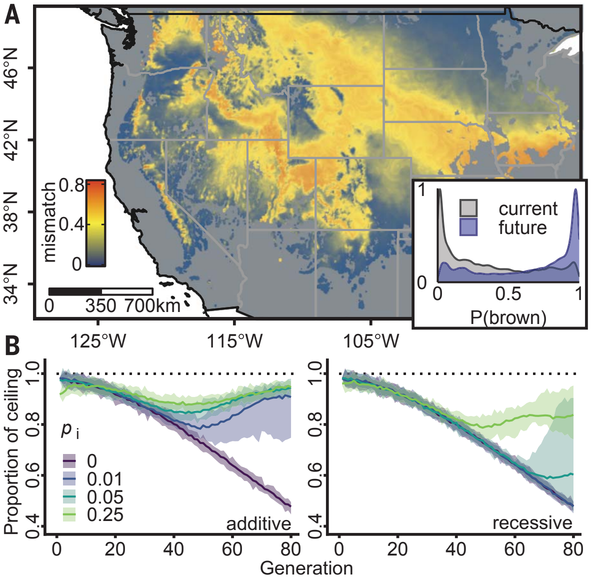

Fig. 4. Adaptation to future climate-induced mismatch. (**A**) Predicted phenotypic mismatch ($\Delta P_{(\mathrm{brown})}$) in 2080 using RCP8.5 forecasts of snow residence time, mean diurnal temperature range, and isothermality (inset: predicted probability shifts toward winter-brown across the USA range). (**B**) Simulated size trajectories of populations (30 replicates; lines, averages; ribbons, 95% quantiles) experiencing future camouflage mismatch ($\Delta P_{(\mathrm{brown})} = 0.75$) shown as a proportion of the population ceiling (dotted line) assuming standing variation of additive (left panel) or recessive (right panel) brown alleles at *CORIN* and *EDNRB*.

To understand how jackrabbit camouflage might evolve in response to climate change, we forecasted winter coat color probabilities for the year 2080 on the basis of correlates of snow residence time, seasonality, and transience (Fig. 4A and fig. S2, D to F). We used forecasts under a high–CO_2 emissions scenario [Representative Concentration Pathway (RCP) 8.5] to model challenging, though not unlikely (*42*), conditions that jackrabbits may experience in the future. Under this model, winter-brown coats ($P_{(\mathrm{brown})} \geq 0.8$) will be strongly favored across much of the southern (USA) range (~49% at $P_{(\mathrm{brown})} \geq 0.8$ in 2080; fig. S2, B to F), a 3.1-fold increase over historical conditions (16% at $P_{(\mathrm{brown})} \geq 0.8$). Although the rate of mismatch will depend on which emissions scenario transpires, future reductions in snow cover are likely to induce widespread camouflage mismatch (Fig. 4A) given strong correlations of forecasted parameters across emission scenarios (*21*).

Previous work proposed that standing variation for seasonal camouflage could promote rapid evolutionary rescue in species threatened by diminished snow cover (*11*). To understand if the genetic basis of camouflage inferred from Colorado populations may facilitate evolutionary rescue more broadly, we sequenced 69 additional white-tailed jackrabbit genomes from across the range (~2.1×; table S14). Although winter phenotypes were mostly unknown for these samples, we found low genetic structure ($F_{ST} = 0.020$ Colorado versus North Dakota) and color-associated polymorphisms outside of Colorado at all three genes (fig. S15). Moreover, the presence of white alleles at the three genes was positively correlated with snow cover duration across the range ($r = 0.33$ to 0.46, $p < 0.05$; fig. S16). Therefore, multigenic color-associated variation appears functionally relevant and broadly shared across the range.

Next, we simulated the capacity for populations with the largest forecasted mismatch ($\Delta P_{(\mathrm{brown})} = 0.75$) to adapt to changes in snow cover. Focusing on large-effect variation at *CORIN* and *EDNRB*, we found that populations without winter-brown alleles trended toward extinction, whereas populations with winter-brown alleles could adapt rapidly. Evolutionary rescue was likely even under a high-emissions scenario and when adaptive winter-brown alleles were initially rare (Fig. 4B and figs. S17 and S18). However, the efficacy of selection depended on genetic dominance. Fully recessive winter-brown variation, as found in other hares (*6*, *32*), was associated with slower responses and larger population declines (Fig. 4B and fig. S18). Thus, the capacity for evolutionary rescue to buffer against future population declines in this and other species confronted by seasonal mismatch (*11*) will depend on local demography, the genetic architecture of adaptive traits, and frequencies of adaptive alleles (*3*).

Toward a framework for prioritizing and facilitating conservation efforts

Optimism that standing variation could enable evolutionary rescue in the face of camouflage mismatch is tempered by widespread population declines in white-tailed jackrabbits caused by habitat alteration, extermination, shifts in predator communities, and climate change (*19*) coupled with the emerging threat of rabbit hemorrhagic disease virus (*43*). Using regional conservation assessments (*19*), we found that populations predicted to harbor winter-brown variation ($P_{(\mathrm{brown})} \geq 0.8$) have disproportionately experienced local declines or extirpations (Pearson's χ^2 test P value = 2.2×10^{-16}; Cramér's $V = 0.31$; fig. S2C). Given these threats, our predictive map of climate-induced camouflage mismatch (Fig. 4A) provides an initial framework for prioritizing conservation efforts. Adaptive potential may be enhanced through local management actions aimed at reducing anthropogenic stressors and promoting connectivity between populations harboring critical winter-brown variation. Our findings also enable quantification of color-associated variation in vulnerable populations by using any DNA source without knowledge of winter phenotypes. In the absence of connectivity or standing variation, our simulations suggest that local adaptation could be accelerated by modest amounts of human-assisted gene flow to mismatched populations (*44*).

Safeguarding the adaptive potential of populations is central for conservation (*1*), yet the genetic basis of adaptation is rarely incorporated into applied conservation planning (*11*, *45*). Landscape genomic approaches have proven useful for uncovering adaptive genetic variation and climate change vulnerability without knowledge of phenotypes (*46*, *47*). Our results show why a deeper understanding of the genetic basis of adaptive traits may also be needed to predict future responses of populations threatened by climate change and how such insights may be applied to facilitate evolutionary rescue.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S18
Tables S1 to S14
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MDAR Reproducibility Checklist

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The evolution of white-tailed jackrabbit camouflage in response to past and future seasonal climates

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Mismatch fix
A wide array of mammal species have adapted seasonal coat color change, shifting from brownish summer coats to white-ish winter coats to match their environment. Climate change has already begun to affect the extent and timing of snow cover, leaving many individuals and populations now mismatched to their backgrounds for part of the year. Ferreira *et al*. looked at the genetics underlying these coat color changes and their variation across populations in white-tailed jack rabbits. Patterns of variation at three specific genes drove coat color change and differed across populations. Models suggest that standing variation across these genes and populations may allow for rapid adaptation to reduced snow cover and browner coats in this species. —SNV

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