EVOLUTIONARY BIOLOGY

Adaptive introgression underlies polymorphic seasonal camouflage in snowshoe hares

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Snowshoe hares (*Lepus americanus*) maintain seasonal camouflage by molting to a white winter coat, but some hares remain brown during the winter in regions with low snow cover. We show that cis-regulatory variation controlling seasonal expression of the *Agouti* gene underlies this adaptive winter camouflage polymorphism. Genetic variation at *Agouti* clustered by winter coat color across multiple hare and jackrabbit species, revealing a history of recurrent interspecific gene flow. Brown winter coats in snowshoe hares likely originated from an introgressed black-tailed jackrabbit allele that has swept to high frequency in mild winter environments. These discoveries show that introgression of genetic variants that underlie key ecological traits can seed past and ongoing adaptation to rapidly changing environments.

Many species undergo reversible changes in morphology, physiology, and behavior to cope with the challenges of seasonal environments. These critical components of phenotypic plasticity often track the environment through the photoperiod-dependent release of hormones (*1*). However, circannual rhythms can become desynchronized when abiotic conditions change rapidly (*2*), leading to declines in population fitness (*3*). The capacity of species to adapt to rapidly changing environments will depend in part on the proximate and ultimate causes of variation underlying seasonal traits (*4*, *5*), which remain poorly understood at the molecular level (*1*, *2*).

At least 21 bird and mammal species undergo autumn molts from brown to white coats (*6*–*8*) as part of a suite of plastic trait responses to seasonal environments. We used natural variation in seasonal camouflage of the snowshoe hare (*Lepus americanus*) to understand the genetic basis of this critical seasonal trait. Autumn molts to white winter coats are cued by photoperiod (*8*) and generally track seasonal snow cover (*7*). Direct estimates of hare survival have shown that mismatch between coat color and snow cover increases predation (*3*). White winter coats predominate across the snowshoe hare range, but some populations molt into brown winter coats (Fig. 1). In the Pacific Northwest (PNW), shifts in the probability of white coats coincide with a gradient in snow cover from warmer coastal to colder inland environments, consistent with local selection for seasonal camouflage, with color morphs co-occurring across a broad polymorphic zone (Fig. 1C) (*7*).

To dissect the genetic basis of polymorphic seasonal camouflage, we used whole-genome sequences for a winter-white hare from Montana (MT, 33x coverage) (*9*, *10*) and a winter-brown hare from Washington (WA, 22x coverage) and constructed a reference through iterative mapping (*11*) to the rabbit genome (*9*, *12*). We then sequenced 80 whole exomes (62 Mb, 21 ± 7.6x coverage per individual) from two regions in the PNW polymorphic zone (WA, n = 26; Oregon, hereafter OR, n = 26; each region 50% winter-white), a monomorphic winter-white locality in MT (n = 14), and a monomorphic winter-brown locality in British Columbia (BC, n = 14; table S1). If the polymorphic zone represents admixture between previously isolated populations, then genetic structure could obscure genotype-phenotype associations (*13*). Analysis of 38,694 unlinked single-nucleotide polymorphisms (SNPs) revealed geographic structure (Fig. 1C), but genome-wide genetic differentiation (fixation index, F_{ST}) between winter-brown and winter-white individuals was ~0 within polymorphic localities (table S2). The polymorphic zone also showed no evidence of admixture on the basis of linkage disequilibrium patterns (fig. S1) or allele sharing with other populations (table S3) (*14*). Thus, geographic variation for winter coat color in the PNW likely reflects primary intergradation across a gradient in snow cover.

We tested 513,812 SNPs for coat color associations across polymorphic populations and identified a single outlier region on chromosome 4 in perfect association with winter coat color ($P = 4.24 \times 10^{-10}$, dominant association test; Fig. 2A, fig. S2, and data S1) (*12*). We then augmented exome data with low-coverage whole-genome resequencing of polymorphic zone hares (~20x per color morph). Coat color associations based on genotype likelihoods (15,173,804 SNPs) (*15*) confirmed a single outlier region (fig. S3) localized to a ~225-kb interval of elevated F_{ST} between color morphs. This interval was centered on the pigmentation gene *Agouti* and two flanking genes, *Ahcy* and *Eif2s2*, neither of which are known to be directly involved in coat color (Fig. 2B). Winter-brown hares were homozygous (n = 26) for brown-associated alleles (hereafter *a*), whereas winter-white hares were either heterozygous (n = 24) or homozygous (n = 2) for the alternative allele (hereafter *A*; Fig. 2C). We then induced autumn molts in 18 captive wild-caught hares (WA, n = 11; MT, n = 7) and found perfect concordance between *Agouti* genotypes and winter coat colors (Fig. 2C and table S4). This experiment included a heterozygous (*Aa*) wild-caught winter-white female from WA that gave birth in captivity to both winter-white and winter-brown offspring (Fig. 2D). Therefore, winter coat color segregates as a dominant locus in both wild and captive animals.

The agouti signaling protein (ASIP) antagonizes the melanocortin-1 receptor (MC1R) in follicular melanocytes, shifting melanogenesis toward lighter pheomelanin pigments or inhibiting pigment production (*16*). MC1R mutations suppress expression of winter-white coats in dark or blue color morphs of arctic foxes, suggesting that ASIP-MC1R interactions are involved in the development of seasonal color molts (*17*). *Agouti* is typically expressed as ventral- or hair cycle–specific isoforms distinguished by alternative 5′ untranslated regions (5′UTRs; Fig. 2B) (*18*). Both isoforms have been associated with lighter dorsal pelage (*19*, *20*). We hypothesized that the development of winter-white coats, which mostly lack pigments (*8*), is controlled by isoform-specific up-regulation of *Agouti* during the autumn molt. To test this, we quantified allele-specific expression of both isoforms and the tightly linked *Ahcy* locus in dorsal skin biopsies from three captive heterozygous hares (*Aa*) undergoing brown-to-white molts. Quantitative polymerase chain reaction (qPCR) verified expression of *Ahcy* and the *Agouti* hair-cycle isoform, whereas expression of the ventral isoform was negligible (Fig. 3A and tables S5 and S6). Targeted pyrosequencing revealed highly skewed expression toward the white (*A*) allele of the *Agouti* hair-cycle isoform ($P < 0.0001$, Student's t test), indicative of cis-regulatory variation, whereas *Ahcy* showed equal allelic expression (Fig. 3B and table S7). These data suggest that winter-white coats develop because of increased expression of *Agouti* during the autumn molt, which fits with our observed dominance relationships and previous studies on the evolution of lighter pelage in deer mice (*19*, *20*). Our findings directly link *Agouti* expression and the evolution of seasonal

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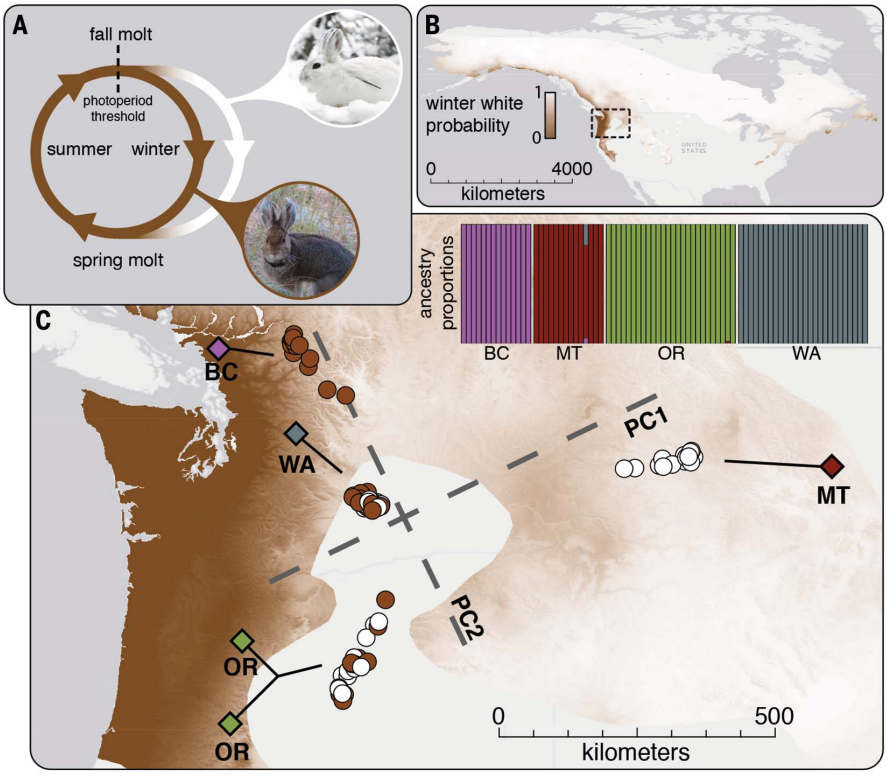

Fig. 1. Winter coat color polymorphism and population structure in snowshoe hares. (**A**) Alternative winter color morphs in snowshoe hares. [Photo credit: L. Scott Mills research photo] (**B**) The modeled range-wide probability of winter-white coats, adapted from (*7*). (**C**) Magnification of region outlined in (B) shows principle components (PC1, 7.42%, and PC2, 5.27%; coat color represented as brown and white circles) and population ancestry plots of 38,694 unlinked SNPs derived from 80 exomes sampled from five localities (colored diamonds) overlaid on the probability of winter-white coats in the PNW.

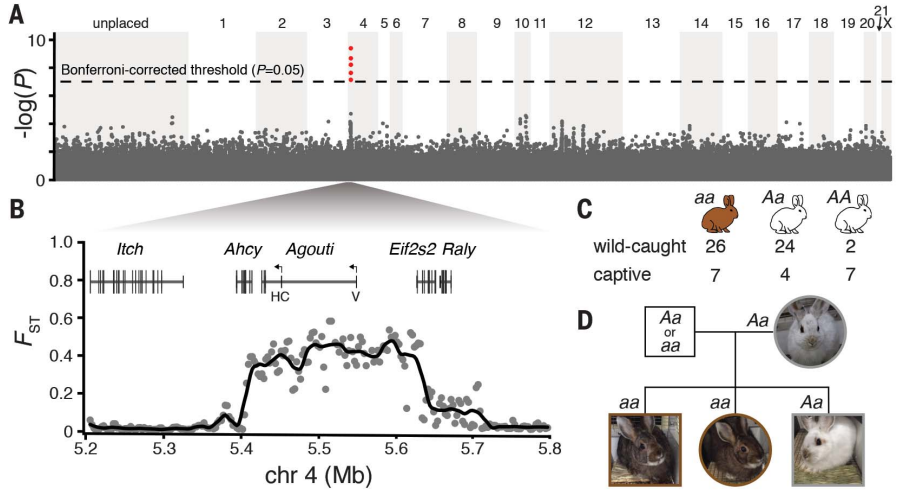

Fig. 2. The genetic basis of winter coat color polymorphism. (**A**) Exome SNP associations ($-\log_{10}$ of *P* values, assuming dominant minor allele; 513,812 SNPs) for polymorphic zone individuals. Red points above the dashed line exceed the Bonferroni-corrected threshold of $P = 0.05$. (**B**) Gene structures of *Itch*, *Ahcy*, *Agouti*, *Eif2s2*, and *Raly* across the associated interval on chromosome 4 (chr 4) and alternative *Agouti* transcription start sites (arrows) corresponding to hair-cycle (HC) and ventral (V) 5′UTRs. Sliding window averages of F_{ST} (5 kb with 2.5-kb step) between winter-white and winter-brown individuals with low-coverage whole genomes (15,173,804 SNPs). (**C**) Dominance of winter coat color inferred from *Agouti* genotypes of wild (OR and WA; Hardy-Weinberg $\chi^2 = 1.6$, $P = 0.21$) and captive (WA and MT) hares. (**D**) Pedigree and genotypes of a mixed-phenotype family (paternal genotype is unknown but inferred to carry the *a* allele). [Photo credit: Diana J. R. Lafferty and Matthew R. Jones]

camouflage in snowshoe hares and suggest that cis-regulatory evolution plays an important role in the origin of seasonal traits.

Comparison of winter-white (MT) and winter-brown (WA) genomes revealed notably elevated levels of absolute genetic divergence across *Agouti* (*Agouti* $d_{XY} = 1.6\%$; genome-wide $d_{XY} = 0.41\%$; $P < 0.0001$, randomization test; Fig. 4A and fig. S4), indicating that the color polymorphism did not arise from a recent de novo mutation. Alternatively, elevated divergence could reflect either the long-term maintenance of polymorphism or introgression from another species (*21*, *22*). Six of the 32 species of hares and jackrabbits (genus *Lepus*) have winter-white molts, but evolutionary relationships within this rapid radiation are poorly resolved (*23*). To examine the origins of winter coat color variants, we combined whole-genome sequences of two additional winter-white snowshoe hares from Pennsylvania and Utah, two winter-brown black-tailed jackrabbits (*L. californicus*) from Nevada, and a previously sequenced winter-white mountain hare (*L. timidus*) from Europe (*10*). Phylogenetic analyses (*24*) predicted a very rare topology at *Agouti* that clustered individuals by winter coat color (Fig. 4B and fig. S5). Pairwise divergence between all winter-brown and winter-white individuals was significantly elevated across a known cis-regulatory region of *Agouti* (*25*, *26*) ~40-kb upstream of the transcription start site of the hair-cycle isoform ($P < 0.001$, randomization test; Fig. 4A and fig. S4). Divergence peaked across a ~20-kb interval ($d_{XY} = 2.2$ to 2.4%) that included a 1033-base insertion on the winter-white haplotype and a ~4.3-kb deletion on the winter-brown haplotype (fig. S4). Additional functional data are needed to determine if either of these candidate mutations underlie the observed cis-regulatory differences in *Agouti* expression (Fig. 3B).

The elevated interspecific divergence between color groups suggests that the winter-white and winter-brown *Agouti* alleles may have arisen relatively early in *Lepus* (*21*). By contrast, divergence within color groups was strongly reduced across a larger interval encompassing *Agouti* (Fig. 4A and fig. S6), indicating that winter coat color alleles may have been shared through hybridization. In support of this hypothesis, we found low, but significant, levels of genome-wide introgression (*27*) between snowshoe hares and both black-tailed jackrabbits and mountain hares (table S8). Window-based analyses of absolute divergence and derived-allele sharing (*28*) identified the *Agouti* interval among the strongest genome-wide signatures of introgression in both winter-brown and winter-white clusters (fig. S7).

Previous studies demonstrated mitochondrial DNA introgression from black-tailed jackrabbits, a western North American prairie-scrub species, into PNW snowshoe hares and speculated that hybridization may have contributed to the evolution of brown winter coats in snowshoe hares (*29*, *30*). Consistent with this, winter-brown snowshoe hares unambiguously nested within black-tailed jackrabbit variation at *Agouti* (Fig. 4B and fig. S5B), resulting in a 174-kb interval of

significantly reduced divergence between species (d_{XY} = 0.42 versus 1.2% genome-wide; P < 0.001, randomization test) embedded within a 236-kb interval of significant admixture (proportion of introgression, $\hat{f}_{hom}$ = 0.71; Fig. 4A). Strong selection at a locus in the ancestral population can reduce divergence between species (*31*), resulting in false inferences of introgression (*28*); however, coalescent simulations of shared polymorphism with and without selection in the ancestral population indicate that such shallow divergence is highly unlikely in the absence of interspecific gene flow (Fig. 4C and fig. S8). We also detected introgression within the winter-white *Agouti* group (figs. S7 and S8). Resolving the origin and functional relevance of the winter-white signatures awaits further investigation, given that three other North American *Lepus* species undergo some degree of seasonal coat color change (*7*).

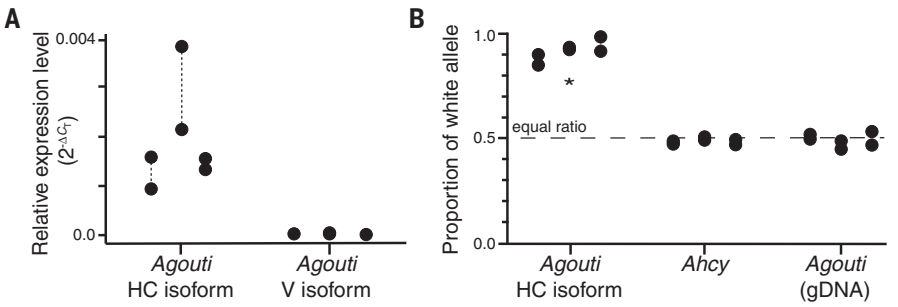

Fig. 3. *Agouti* expression in snowshoe hares during autumn molts. (**A**) The relative expression level ($2^{-\Delta C_T}$, where ΔC_T is the difference in the qPCR cycle threshold relative to *Gapdh*, a constitutively expressed control gene) of hair-cycle (HC) and ventral (V) *Agouti* isoforms in molting skin of winter-white (*Aa*) snowshoe hares. (**B**) Relative abundance of the winter-white allele in the same skin samples for *Agouti* hair-cycle transcripts, *Ahcy* transcripts, and *Agouti* genomic DNA (gDNA). The asterisk indicates that white-allele proportions were significantly increased in *Agouti* transcripts compared to *Ahcy* transcripts and *Agouti* genomic DNA (P < 0.00001, Student's t test). Pairs of points represent technical replicates.

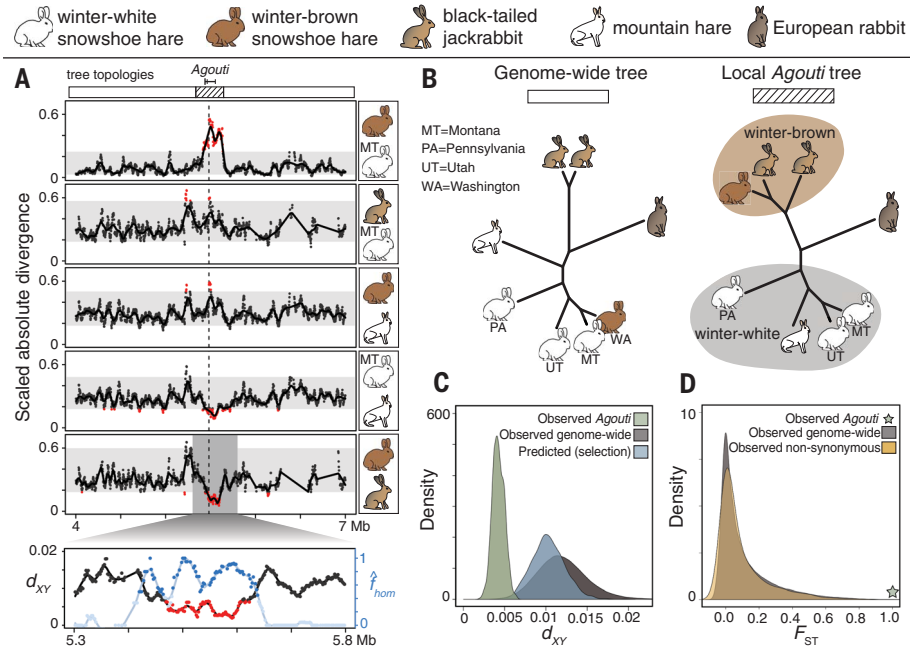

Fig. 4. The evolution of winter coat color alleles in hares and jackrabbits. (**A**) Estimated tree topologies across the *Agouti* region [top, see (B)]. Pairwise comparisons of mutation-scaled absolute genetic divergence in 20-kb sliding windows (dashed line indicates location of candidate insertion-deletion mutations). Gray rectangles represent 99.8% bootstrap quantiles, and red points are windows with one-tailed P < 0.001 based on randomization tests. Bottom plot shows a finer scale of absolute divergence in black (d_{XY}, red points with one-tailed P < 0.001) and the fraction of introgression in blue ($\hat{f}_{hom}$, dark blue points with z score > 4) between black-tailed jackrabbits and the WA winter-brown snowshoe hare. (**B**) The most common genome-wide topology (white) and the local *Agouti* topology (hatched; rabbit outgroup). Brown- and gray-shaded regions indicate winter-brown and winter-white groups, respectively. (**C**) Distributions of d_{XY} between the winter-brown snowshoe hare and black-tailed jackrabbits genome-wide (gray), at *Agouti* (green), and under simulations of strong ancestral selection (blue). (**D**) Distributions of SNP F_{ST} values between BC (monomorphic winter-brown) and MT (monomorphic winter-white) hares genome-wide (gray) and for nonsynonymous SNPs (yellow). The green star indicates F_{ST} = 1 at a diagnostic *Agouti* SNP.

To link introgression with local adaptation, we tested for selective sweeps on the basis of allele frequency skews (*32*) while controlling for demographic history (fig. S9 and table S9). We detected a hard sweep overlapping *Agouti* in winter-brown individuals from the polymorphic zone but no evidence for a sweep in winter-white individuals (figs. S10 and S11). We estimate that the sweep of the winter-brown allele in the PNW occurred 3000 to 15,000 years ago, after the retreat of the Cordilleran ice sheet (*33*). High inferred selection coefficients (s) on the introgressed winter-brown *Agouti* background ($\overline{s_{WA}}$ = 0.024, $\overline{s_{OR}}$ = 0.015; fig. S11C) and fixation of alternative *Agouti* alleles between monomorphic winter-brown (BC) and winter-white (MT) localities (Fig. 4D), despite high gene flow (table S9), indicate that seasonal camouflage is maintained under strong local selection.

Despite widespread evidence of hybridization between animal species, introgression has rarely been directly linked to ecological adaptation (*34*–*36*). We have shown that introgression has shaped locally adaptive seasonal camouflage in snowshoe hares. Recurrent introgression of coat color variants could facilitate evolutionary responses to environmental change within populations as well as the long-term maintenance of adaptive variation among species, similar to adaptive polymorphisms of beak morphology across the radiation of Darwin's finches (*22*, *34*). The evolution of winter-brown coats in snowshoe hares may have enabled their persistence in environments with more ephemeral seasonal snow after the end of the last glacial maximum. Temperate snow-cover duration is predicted to dramatically decrease over the next century under most models of climate change (*37*), which may further intensify directional selection for winter-brown camouflage (*3*, *6*). Thus, the establishment of this dynamic color polymorphism through introgression is likely to be a critical component of ongoing adaptation to rapidly changing seasonal environments (*7*) in this iconic ecological model.

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Competing interests: None declared. **Data and materials availability:** Original sequence data are available in the Sequence Read Archive (www.ncbi.nlm.nih.gov/sra) under BioProject PRJNA420081 (SAMN08146448 to SAMN08146534). Previously generated whole-genome sequence data of snowshoe hare (SAMN02782769 and SAMN07526959) and mountain hare (SAMN07526960) are also available in the Sequence Read Archive.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/360/6395/1355/suppl/DC1
Materials and Methods
Figs. S1 to S11
Tables S1 to S9
References (*38*–*82*)
Data S1

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Hybrid camouflage variation

Snowshoe hares molt from a brown coat to a white coat in winter. In some populations, however, where winter snow is less extensive, hares molt from a brown coat to a brown coat. Jones *et al.* show that regulation of the pigmentation gene *Agouti* is responsible for the winter coat color change. Hybridization with jackrabbits has led to introgression around this gene that facilitates the brown winter morph. Hybridization appears to have provided important adaptive variation to the snowshoe hare.

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