point. As with LiP-MS, TPP allows for the rapid quantitation of thousands of proteins, in this case, with respect to their folding stability upon an increase in temperature. The change in melting point can reveal the binding of a small molecule or protein, but in contrast to LiP-MS, TPP does not inform on the location of the structural change.

Even more excitingly, the new work also illustrates how investigators are beginning to integrate several omics approaches to gain new insights from complementary data. Other such examples include the combination of LiP-MS with TPP and MS (Leuenberger et al., 2017) or the integration of proteomics with transcriptomics and translatomics data (Jovanovic et al., 2015) (Rendleman et al., 2018). This new form of exploration creates another field, that of “integromics” (Vitrinel et al., 2019), which represents another step toward understanding how molecules and their arrangements create the next level up in biological organization, that of the entire cell.

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Fishing for the genetic basis of migratory behavior

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For many species, migrating at just the right time is essential for both survival and reproduction. A new study in salmon localizes a small genomic region associated with migration timing, which in turn affects other physiological traits, suggesting that a seemingly complex suite of migration traits is linked by one “simple” phenotype.

Migration, the seasonal movement of animals from one habitat or region to another, occurs in nearly all major animal groups—from the iconic humpback whale that breeds in the tropics and then heads 9,000 km north to its feeding ground to the monarch butterfly whose migration is longer than its lifespan, so no one butterfly makes the entire trip. There exists striking variation in migration patterns even within species, which can be accompanied by changes in physiology, morphology, and/or other behaviors, often demarcating distinct migration “ecotypes.” The tight link between migration pattern and other phenotypes is best exemplified by the approximately 100 species of diadromous fish that migrate between saltwater and freshwater. Chinook salmon, for example, exhibit multiple migratory ecotypes that repeatedly co-occur in rivers across the northwestern United States: early (winter and spring) migrators have higher fat contents, earlier spawning times, and smaller body sizes than late (fall and late fall) migrators. A new study by Thompson et al. (2020) narrows in on the genetic basis of migration timing in salmon, shedding new light on how migration ecotypes evolve.

Due to the seemingly complex nature of migratory behavior and its associated traits, one may expect many loci across the genome to be involved. However, a series of recent studies suggests otherwise: variation in migration timing in Chinook salmon has a strikingly simple architecture, with only a single genomic region strongly associated with migration behavior (Thompson et al., 2020; Prince et al., 2017; Narum et al., 2018). Using whole genome resequencing of salmon across multiple rivers (Figure 1A), this latest paper (Thompson et al., 2020) refines the locus to a narrow 140-kb region in which SNPs are perfectly associated with spring- versus fall-run fish and an even smaller 30-kb region containing SNPs shared by spring- and winter-run fish (Figure 1B). Genotype at this locus explains 85% of the variance in migration: migration timing of fish homozygous for the "early" haplotype is nearly non-overlapping with that of fish homozygous for the "late" haplotype, and heterozygotes are intermediate (Figure 1C) (Thompson et al., 2020; Prince et al., 2017). These results suggest not only a simple genetic architecture but also a high heritability of migration behavior.

How does a single locus determine migration timing along with the many associated morphological and physiological differences? Correlation analyses show that the region is statistically associated with only timing of freshwater entry and not other ecotype-related phenotypes (e.g., maturity status, fat content) (Thompson et al., 2020). Thus, the authors suggest that a single genetic locus influences migration timing, resulting in an environmental change that, in turn, affects other physiological characteristics. Narrowing in on the causal mutation(s) will help further resolve the specific role of the locus. However, since the region contains many variants, including multiple short duplications, that are strongly associated with the migration-timing, this could be challenging. Promisingly, the locus overlaps with only two known genes, ROCK1, a gene that encodes a protein kinase, and GREB1L, an estrogen-responsive gene (Figure 1B). Even without specific causal mutations, a better understanding of the function of these two genes in salmon may help elucidate the mechanism by which this region determines migration ecotypes.

This simple genetic architecture also provides an explanation for how multiple migratory ecotypes are maintained both within and across rivers. While it was previously thought that within-river ecotypes remain distinct through assortative mating, this study suggests that ecotypes readily interbreed, likely having offspring with different migratory phenotypes due to the Mendelian inheritance of the migration-timing locus. Interestingly, despite the evidence for gene flow among ecotypes, genetic variants within the region remain highly correlated. One possible explanation for this pattern of extended linkage disequilibrium is the presence of a chromosomal inversion. Since inversions can maintain divergence across a region by reducing the frequency of recombination in heterozygotes, they can be hotspots for evolutionary change and have previously been implicated in migratory behavior in fish (Pearse et al., 2019; Kirubakaran et al., 2016) and birds (Lundberg et al., 2017). Although short-read sequencing data did not identify inversion breakpoints in salmon, other approaches such as long-read sequencing may provide more power to detect any chromosomal rearrangements.

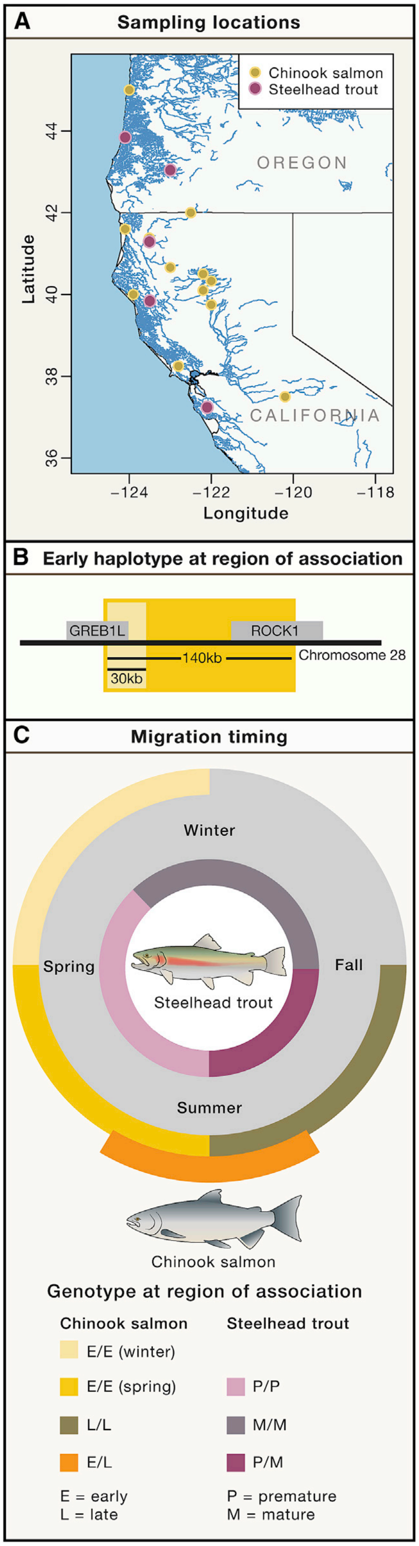

Figure 1. Migration timing in salmon and trout is controlled by the same genetic locus

(A) Approximate sampling locations of Chinook salmon (Thompson et al., 2020) and steelhead trout (Prince et al., 2017) in the northwestern United States.

(B) Chinook salmon migrate from the ocean into freshwater at different times of year, with their migration timing controlled by a single "region of association." The region of association was localized to 140 kb and overlaps with two coding genes, GREB1L and ROCK1. Winter-run salmon share a 30-kb segment of this region with the spring-run salmon.

(C) At the region of association, winter- and spring-run salmon are homozygous for the early haplotype (E/E), whereas fall-run salmon are homozygous for the late haplotype (L/L). Heterozygotes (E/L) migrate during the summer months (i.e., intermediate timing). Migration timing in steelhead trout is associated with the same genomic region; trout homozygous for the premature haplotype (P/P) migrate in spring, trout homozygous for the mature haplotype (M/M) migrate in fall and winter months, and heterozygotes (P/M) migrate during intermediate months.

Similar to Chinook salmon, early and late migrant phenotypes are also observed in other diadromous fish, such as trout. In steelhead trout, a single 200-kb region is strongly associated with migration timing (Prince et al., 2017), and remarkably, this region overlaps with GREB1L, one of the two genes within the implicated locus of salmon. As in salmon, the locus has an additive effect on migration timing (Figure 1C) and likely has a single origin since the ‘‘premature’’ (or early) migration allele is shared across trout found in distinct river drainages. A comparison of salmon and trout shows that haplotypes in this region are more similar between different migration types within species than between equivalent types across species. This suggests that, while the same allele underlies migratory behavior within species, the premature (or early) migration haplotype evolved independently in salmon and trout.

Why is the same region associated with migratory behavior across multiple species? One possibility is that this genomic region is susceptible to mutations, like the ‘‘fragile’’ *Pitx1* locus underlying the repeated loss of pelvic structures in stickleback fish (Xie et al., 2019). Unlike sticklebacks, however, neither salmon nor trout show repeated mutational events within species (Thompson et al., 2020; Prince et al., 2017). Another possibility is that one of the genes in the region has a particularly strong and specific effect on migration. Thus, an even larger question remains: of the many species that show seasonal migration—from whales to birds to butterflies—how often is the same gene or pathway involved? Current studies underway in birds (Toews et al., 2019; Delmore et al., 2016) and butterflies (Merlin et al., 2020) identify genes related to circadian clock regulation, muscle morphology, and neurotransmission linked to migratory behavior, suggesting there may be many possible genetic mechanisms driving the evolution of migration. Yet, as recent findings in fish highlight, perhaps some genomic regions (and even genes) are more commonly implicated in this striking animal behavior than others. To answer this question, we await more similarly comprehensive studies on the genetics of migration.

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