# IDENTIFYING THE LOCATION OF PHOTOTRANSDUCTION GENES IN THE RAINBOW TROUT GENOME

by

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# IDENTIFYING THE LOCATION OF PHOTOTRANSDUCTION GENES IN THE RAINBOW TROUT GENOME

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ABSTRACT

Migration, the long distance movement of animals to take advantage of seasonal resources, has long fascinated scientists and the general public alike. Although much is known about the ecology of migration, little information is known about the genes underlying this behavior. Rainbow trout (*Oncorhynchus mykiss)* contains both migratory and resident individuals. Migrants move to the ocean for up to four years before returning to their natal streams to spawn, whereas resident individuals stay in their natal streams throughout their lives. An individual with migratory parents is more likely to migrate than an individual with resident parents. However, the development of the migratory phenotype also depends on environmental factors, such as food abundance and territory allocation. These factors can cause individuals with migratory parents to become resident if these factors best increase their fitness. Previous studies have found several genes connected to vision and light sensitivity to be differentially expressed between migrants and residents. Nevertheless, the location of these genes in the rainbow trout genome is unknown. To date, unlike the human genome, the rainbow trout genome is incomplete. The purpose of this project was to determine the location of these differentially expressed genes. In so doing, it is hoped that I will be able to determine how inheritance of these genes influence the decision to migrate. This research will help in determine the contribution of genes associated with vision and perception of light on migration in rainbow trout and may provide candidate genes for studies in other migratory organisms.

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TABLE OF CONTENTS

# INTRODUCTION

Migration is a complex phenomenon involving the long distance movement of individuals to take advantage of temporary resources in response to environmental cues (1,2). Migration is observed in various animal groups, such as fish, insects, and birds (3,4). However, the general mechanisms and processes that cause individuals to anticipate adaption to a new environment are not identical across species (4,5,6). This variation between individuals makes understanding an enigmatic life-history strategy all-the-more difficult.

Anadromous species (such as salmonids and lamprey) are born in freshwater, migrate to saltwater, and return to their natal streams to spawn (3). Within the same population of salmonids, both resident and migrant individuals can be present (4), i.e., the population is considered partially migratory. Migratory individuals undergo smoltification to prepare for the marine environment; a process in which an individual incurs physiological, morphological, and behavioral changes in order to survive in a salt water environment (4,8). Some of these necessary changes include increases in lipid metabolism, protein synthesizes, length to weight ratio, and hypo-osmoregulation, changes that are not required of resident counterparts that stay in their natal rivers and streams (9). All rainbow trout (*Oncorhynchus mykiss*) are raised in freshwater streams. Migrants spend up to two years growing in freshwater environments before they undergo the smoltification process (upon which these individuals are known as smolts).

Several quantitative genetic studies have found that migration in rainbow trout is highly heritable, but genetic predisposition is not an absolute predictor for a migrant- or resident-life strategy (5,10). This variation is caused by changes in environmental factors such as water temperature, photoperiod, and water flow. These cues initiate changes in gene expression for many traits associated with the development of the migratory phenotype (7, 11). All rainbow

trout juvenile are identical in appearance until about two years of age when phenotypic differences are observed between resident and migrant fish (12). Individuals that will migrate take on a silvery-appearance, known as steelhead trout (4). The resident juvenile rainbow trout, known as parr, sexually mature to the adult form and remain resident in their natal streams (13).

A critical environmental cue for inducing smoltification and migration in rainbow trout is photoperiod (ie. length of day) (2,6). The pineal gland is a photosensitive organ that assists in establishing biological rhythms in response to light changes (12). With enhanced photoperiod sensitivity in the retina, as well as the pineal gland, smolts perceive and are more sensitive to vision and light patterns compared to parr. Also, melanophores (dermal photoreceptors in the eye) appear to have enhanced sensitivity in smolts compared to parr (12). In gene expression studies, vision sensory and light perception genes, such as rhodopsin, have been found to be upregulated in migrants compared to residents (14). In an experimental study with steelhead trout, deviation from seasonal photoperiod lengths altered departure for migration (15). The overexpression of phototransduction genes presumably helps smolts keep track of the time of the year in order to know when to initiate smoltification, and ultimately, migrate downstream migrate in the late spring/early summer.

Quantitative trait loci (QTL) studies are able to associate genotype-phenotype variation within a population to genomic regions for a trait of interest (16). Further studies aim to identify the specific genes present within or near migratory-related QTLs and allow for the identification of genes responsible for the variation in the phenotypic trait under study. At this time, the sequenced genome of the rainbow trout is incomplete. Multiple genome duplications occurred 400 million years ago in all bony fish and 100 million years ago in all salmonids, and this increase in the amount of genetic material makes sequencing the rainbow trout genome in its

entirety very challenging. With an incomplete genome, linkage mapping approaches, which measure the amount of recombination between polymorphic markers can be used. Linkage maps have been useful in identifying regions of the the rainbow trout genome associated with migratory traits, and have assisted in annotating the existing fragmented genome (7,9,17, 18, 19). These studies suggest genes related to development rate, circadian rhythm, and thyroid function are associated with migration (13).

As the position of phototransduction genes in the rainbow trout genome is currently unknown, the central aim of this study is to locate and map genes related to light perception and vision sensing in the rainbow trout genome previously found to be differentially expressed between migrants and residents (14). The position within the genome will be determined by identifying single nucleotide polymorphisms (SNPs) in an experimental cross used for mapping studies in the past (9,11,20). The proximity of these genes to previously known QTL for migratory traits will contribute to our understanding of the importance of these genes for the migratory phenotype, and the genetic basis of migration for rainbow trout more broadly.

## METHODS

### Candidate Genes and Mapping Progeny

Seventeen candidate genes were selected for mapping based on their function in light perception and vision (see Table 1 for details and references). The mapping family used in this study is an experimental cross between two clonal lines, a maternal resident line and a paternal migrant line. The maternal clonal line is from a hatchery-raised Shasta-like rainbow trout from Oregon State University (Corvallis, OR) known as OSU. The male clonal line is from a hatchery population in Clearwater River at Dworkshak National Fish Hatchery (Ahsahka, ID), known as CW (see [21] for details of these lines). Two $F_1$ individuals were crossed to produce a

recombinant inbred $F_2$ population of 110 individuals, which represents the mapping panel used in this study. This mapping panel has previously been used in studies for mapping genes and traits associated with migration in rainbow trout (9,11,20). At two years of age, the $F_2$ generation was euthanized and physical features connected to their migratory tactic recorded. Migrants were identified by a streamlined silvery appearance (i.e., had undergone smoltification) and resident individuals were identified by a colorfulstreak on the side of their body.

**Sequencing of Candidate Genes**

Expression sequence tags for rainbow trout were obtained from GeneBank or from the literature (14) in order to design primers for sequencing. These sequences were then investigated for single-nucleotide polymorphisms (SNPs) that could be used to map the seventeen candidate genes (see Table 1). DNA amplification was performed for 8-16 samples per gene consisting of 100 ng of DNA, 1.0 μm of each primer, 200 μm dNTPs, 1 × polymerase chain reaction (PCR) buffer, 1.5 mM $MgCl_2$, and 0.5 U of Taq polymerase (Bioline, Taunton, MA). Conditions used for PCR were 3 minutes at 95°C followed by 35 cycles of 30 s at 95°C, 30 s at 58°C, and 30 s at 72 °C. The annealing temperature of 58°C varied depending on the primer set being used (see Table 1). 5 μL of PCR product was stained with 2 μL GelRed DNA stain (Applied Biosystems) and a 1.0% agarose gel electrophoresis was performed to identify and estimate PCR product size. PCR products were cleaned using 2 μL SAP-EXO (Applied Biosystems, Forster City, CA). The thermal cycler consisted of 15 minutes at 37 °C and 15 minutes at 80 °C. Cycle sequencing was performed using with 8 μL BigDye version 3.1 (Applied Biosystems) and cycle sequencing products were sequenced on an ABI 3130*xl Genetic Analyzer*.

**SNP Identification and Genotyping**

Forward and reverse sequences were aligned using Sequencher version 5.4.6 (GeneCodes, Ann Arbor, MI). SNPs were identified and chosen for further study if they were homozygous for different alleles in both Clearwater and OSU and heterozygous in $F_1$ generation. SNPs were genotyped in the 110 samples in the $F_2$ generation using ABI Prism SNaPshot Multiplex Kit (Applied Biosystems) with SNP-specific primers. Genotypes were scored using GeneMapper version 5.0 (ThermoFisher Scientific, Richardson, TX).

**Linkage Mapping**

Linkage maps were built by combining the genotypes determined in this study with the 372 previously published loci for this same experiment cross (11). JoinMap v 4.1 (Kyazma, Wageningen, Netherlands) was used to build a linkage map with a minimum log of the odds (LOD) score of 4.0. The LOD score is the chance of incorrectly assigning linkage between markers and a minimum score of 4.0 reports a 1 in 10,000 chance of assigning incorrect linkage. Marker order was checked using maximum likelihood, and the most likely marker order for each linkage group was determined. The 110 individual maps were combined to determine the most likely position of the loci of the marker based on the recombination frequency (11). Linkage maps were drawn using MapChart v 2.0.

**Contingency Analysis**

A binary genotype analysis for the identified residents and migrants of the $F_2$ generation of the mapping family was performed. This analysis looked for an association between the allele at each mapped gene and the corresponding phenotype. In other words, did most of the smolts have the allele from the migratory parent (CW), and did most of the residents have the allele from the resident parent (OSU), or was there no association between genotype and phenotype.

Table 1: Candidate genes related to vision and light sensory suspected to be associated to migration.

| Gene | Abbreviation | Function | Reference | PCR Annealing Temperature |
|---|---|---|---|---|
| *Rhodopsin* | *Rho* | Located in rod photoreceptors and assists in light processing in dim light | 22 | 58.0 °C |
| *Opsin SWS1* | *SWS1* | Cone pigment sensitive to short-waves in the violet-ultraviolet from 355-440 nm | 23 | 63.5 °C |
| *Opsin SWS2* | *SWS2* | Cone pigment sensitive to the blue-violet light from 410-490 nm | 23 | 56.0 °C |
| *Opsin RH2* | *RH2* | Cone pigment in the middle-wave class sensitive in the green spectrum from about 480-535 nm | 23 | 58.8 °C |
| *Opsin LW* | *LW* | Cone pigment of long- to middle- wave class maximally sensitive in the spectral region from 490-570 nm | 23 | 58.0 °C |
| *Retinoic acid 6 (STRA6)* | *STRA6* | Cell-surface receptor for retinol-RBP that removes retinol from retinol-binding protein and transports it across the cell membrane into the cell | 24 | 57.1 °C |
| *Arrestin3* | *ARR3* | Inhibits phosphorylated receptor-G protein interaction when in phototransduction cascades | 25 | 62.0 °C |
| *Recoverin* | *RCVRN* | Inhibits rhodopsin kinase Grk1 in dim light when there is high $Ca^{2+}$ | 26 | 65.0 °C |
| *Orthodenticle homeobox 2* | *OTX2* | Transcription factor within the bicoid-subclass of genes involved in head and eye development | 27 | 60.0 °C |
| *Retinol Binding Protein 1* | *RBP1* | Assists in the transfer of retinol between the pigmented epithelium and the photoreceptors | 28 | 56.0 °C |
| *Peripherin 2* | *PRPH2* | Transmembrane glycoprotein located at the base of rod and cone photoreceptors on the outer segments | 29 | 58.0 °C |
| *Guanylate cyclase 2F* | *GUCY2F* | Located in photoreceptors and synthesizes cyclic GMP | 30 | 55.0 °C |
| *Phosphodiesterase 6G* | *PDE6G* | Serves as a protein to deactivate cyclic AMP in phototransduction cascades | 31 | 58.0 °C |
| *S-antigen* | *SAG* | Photoreceptor-specific protein, found in pinealocytes | 32 | 55.0 °C |
| *Retinal pigment epithelium 65* | *RPE65* | Monolayer epithelium adjacent to and partly enclosing photoreceptor cells | 24 | 58.0 °C |
| *Peropsin* | *RRH* | Pigment-like protein that is located in the apical microvilli of the RPE | 34 | N/A |
| *11-cis Retinol Dehydrogenase* | *RDH5* | Located in the retinal pigement epithelium in photoreceptors and converts 11-*cis* retinol to 11-*cis* retinal | 35 | 62.2 °C |

## RESULTS

The locations of 6 out of the 17 candidate genes (see Table 1) were determined based on SNPs that segregated between the clonal lines. The six genes whose location was determined were *Opsin SWS2*, *Retinol Binding Protein 1 (RBP1)*, *Arrestin 3 (ARR3)*, *Retinal Pigment Epithelium 65 (RPE65), Phosphodiesterase 6G (PDE6G)*, and *Orthodenticle Homeobox 2 (OTX2)* (Figure 1). Using the linkage map previously published in Hale et al. (2014), the location of these genes in the rainbow trout genome were determined. One gene, *peropsin*, was unable to be sequenced, and therefore no SNP identification occurred. Of the ten remaining genes, gene regions were successfully sequenced, but SNPs were not identified between the clonal lines of the mapping panel. One of these genes unable to be sequenced was *rhodopsin*.

*Rhodopsin* is involved in the vision transduction cascade, but the gene was found to contain no SNPs. This is most likely because *Rho* contains no introns (35). *OTX2* and *RPE65* are located on chromosome 8. *OTX2* is a transcription factor involved in craniofacial development and *RPE65* is involved with metabolism. Chromosome 8 is of interest as it contains QTL for migratory related traits (9). *Opsin SWS2* is located on chromosome 13 and no migratory-related QTLs have been found on this chromosome. *ARR3* is located on chromosome 29 and does not contain any QTL for smoltification traits. *RBP1* is located on chromosome 2 and contains no QTLs. *PDE6G* is involved in hydrolysis of cyclic nucleotides and is located on chromosome 12. At this time, none of the mapped genes fall within a QTL for migratory-related traits published in Hale et al. (2014).

From the binary genotype analysis, no mapped candidate genes revealed an association between the genotype and phenotype. Using a $\chi^2$ contingency analysis ($\alpha = 0.05$, 1 degree of freedom) with the null hypothesis being that there was no association between alleles at the

mapped markers and the development of different migratory strategies. *Otx2* had an observed value ($\chi$ = 0.58) below than the critical value of 3.84, which suggests the allele distribution is not statistically significant from what would be expected. The remainder of the genes also had observed values below the critical value. *Opsin SWS2* observed value was $\chi$ = 2.87. *RBP1* observed value was $\chi$ = 0.61. *Arr3* observed value was $\chi$ = 0.13. *RPE65* observed value was $\chi$ = 1.14. *PDE6G* observed value was $\chi$ = 1.84.

Figure 1: Locations of the six candidate genes successfully mapped to the rainbow trout genome.

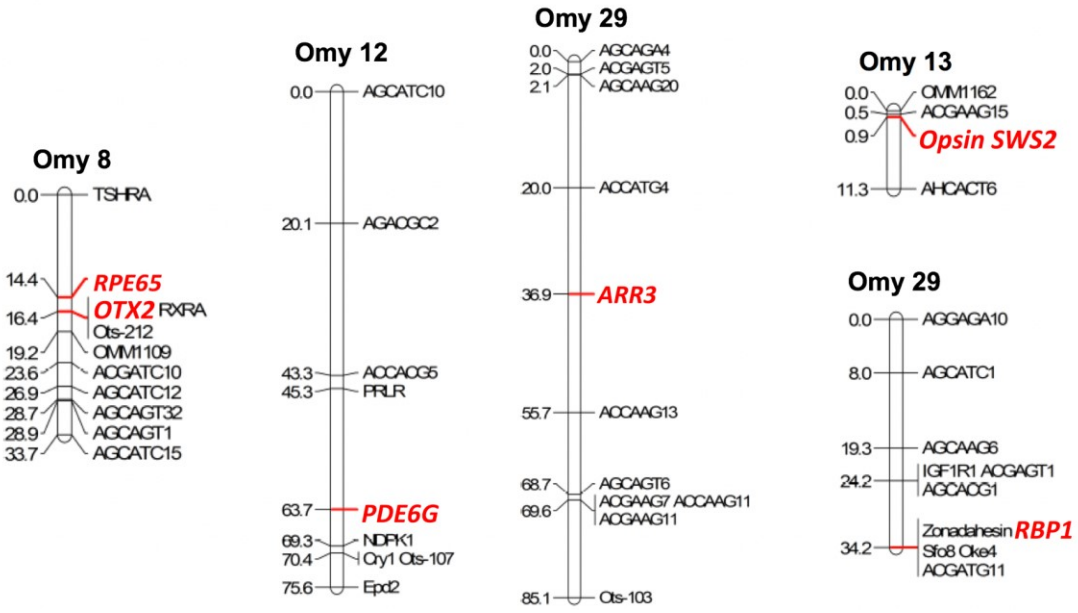
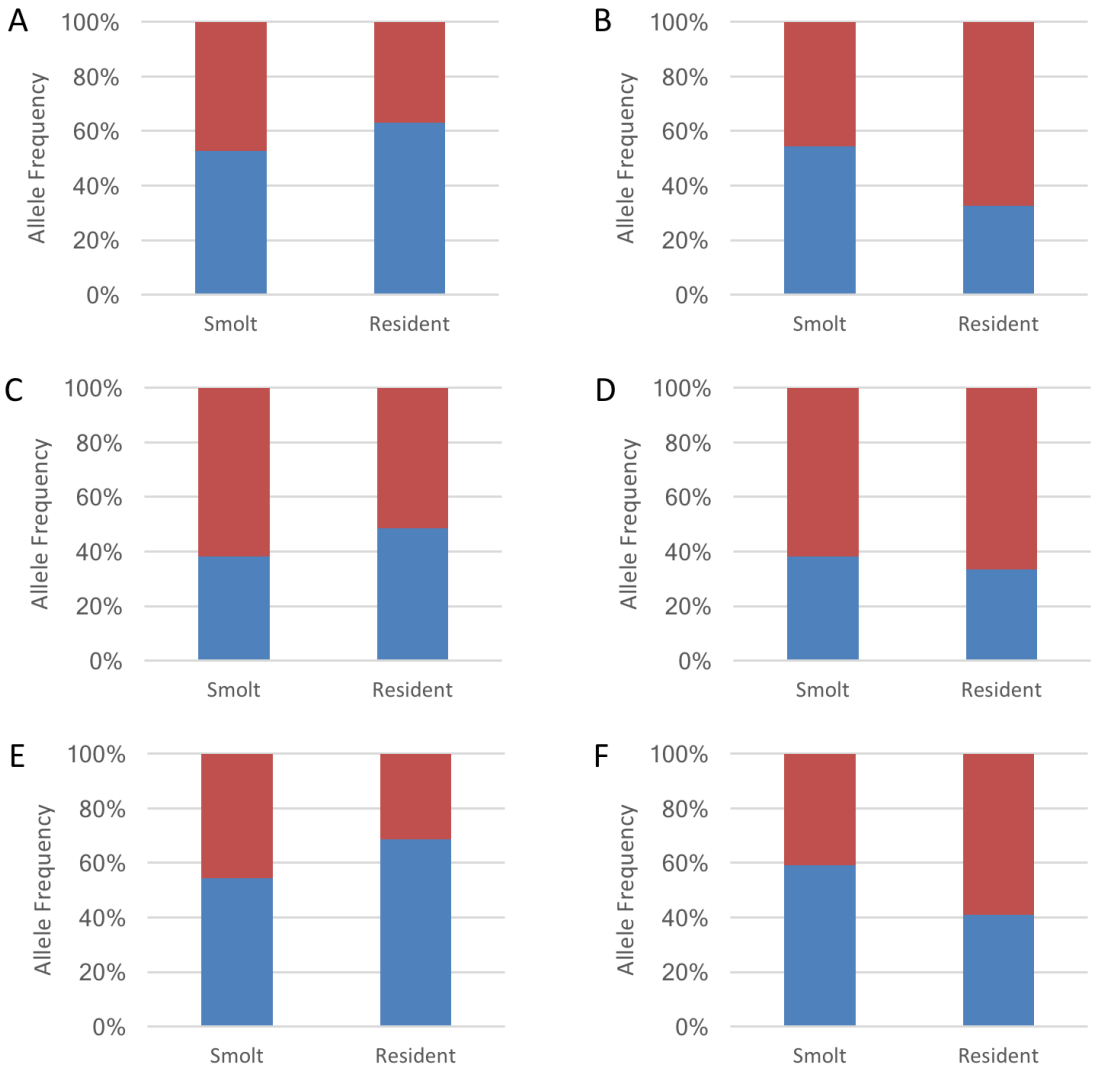



Figure 2: Resident and migrant binary analysis for the six mapped phototransduction genes. The color represents the which parent the allele was inherited from. Blue is from OSU (resident) and red is from CW (migrant). A. *OTX2* B.*Opsin SWS2*, C. *RBP1*, D. *ARR3*, E. *RPE65*, F. *PDE6G*




## DISCUSSION

SNPs in six of the seventeen phototransduction gene regions sequenced were identified and successfully added to the Hale et al. (2014) rainbow trout linkage map, totaling 376 biomarkers. The phototransduction genes mapped in this study are located in regions of the rainbow trout genome not found to be associated within QTLs of migratory-related traits within the OSU x CW experimental cross (14). Also, there does not appear to be an allele-specific association for mapped phototransduction genes for either the resident or migrant life trajectory

decisions, suggesting which allele an individual inherits for these phototransduction genes is not a good predictor for whether they will become a resident or a migrant.

A possibility as to why the location for only six of the candidate genes for linkage mapping was identified could be due to primer design using protein-coding regions as a template, because these sequences are more likely to be conserved between individuals and therefore less likely to contain a SNP. In this study, primers were initially designed from publically available expression sequence tag (EST) sequences on GeneBank and *O. mykiss* brain transcriptome data (14). Individuals of the same species are genetically 99.9% identical, so identifying SNPs in protein-coding regions is less likely than sequencing non-coding protein regions of the genome because negative selection for mutations in protein-coding regions is much more stringent than in non-coding regions.

On chromosome 8, *RPE65 and OTX2* link closely to one another, which indicates it is less likely that recombination during meiosis will occur between these two markers and alleles for these genes will often be associated with one another. The function of *RPE65* is to produce an epithelial layer that lines photoreceptors and *OTX2* codes for a protein involved in head and eye development. Their functions are both essential for proper eye development and function, suggesting their close location to one another on chromosome 8 is essential for smolts, since these genes are upregulated at two years of age when they are departing for migration. Since photoperiod, or day length, is a driving stimulus for the departure to migrate in smolts, the proper function of these phototransduction genes is critical for the interpretation of the time of the year, and therefore completion of the migratory life tactic.

In addition, there is evidence of population level control in the migratory decision. For example, a linkage mapping study crossing a resident and a migrant parent from Sashin Creek,

Alaska created a linkage map for traits linked to smoltification. In Hecht et al. (2012), migratory-related QTLs were identified on chromosomes 8, 12, and 13. On chromosome 8, *OTX2* and *RPE65* were found to also be located on this chromosome, suggesting their close location to a QTL related to migration and their close proximity to one another is essential for the migratory tactic. In addition, *Opsin SWS2* mapped onto chromosome 13 and *PDE6G* was found to be located on chromosome 12. Chromosome 12 is of interest for migratory-related traits in this population, because Hecht et al. (2012) found seven migratory-related QTLs overlapping with *PDE6G*'s genomic location. *Phosphodiesterase 6G* (*PDE6G*) codes for a deactivation protein for cyclic AMP and is exclusively expressed in photoreceptors (31). This infers *PDE6G* function, interpreting the photoperiod stimulus for departure to migrate, is possibly associated with the migratory-related traits found on chromosome 12. Also, this finding further suggests that chromosome 12 could be an area of further interest for better understanding the genetic basis of migration in *O. mykiss*.

More phototransduction genes need to be mapped to the *Oncorhynchus mykiss* genome to determine whether vision and photosensory genes fall closely located to other migration-related traits. SNPs for *Opsin SWS1* and *11-cis Retinol Dehydrogenase* have been identified in this mapping panel, but have not been mapped to the *O. mykiss* genome at the time of publication. In determining their location, stronger conclusions can be made regarding the importance of phototransduction gene location relative to migratory-related QTLs and their determination in life history trajectory.

Although we did not find associations between phototransduction genes and major QTL for migratory-related traits within this population, this does not mean these genes are not consequential in the migratory decision. Other genetic controls could play a role in life tactic

determination in *O. mykiss*. Cis- and trans-factors, such as enhancers and transcription factors, respectively, could influence gene expression that would influence a parr into maturing into a resident or migrant. For example, in Hecht et al. (2012), chromosome 12 contained seven different migratory-related QTLs that could be influenced by cis control, such as shared promoters and enhancers. Although this could be a population specific effect, since this study involved crossing two individuals from a population in Alaska (Sashin Creek), this suggests there is a strong cis effect on the development of migration on this chromosome. In addition, epigenetic controls, such as methylation in promoter regions and acetylation of histones, could alter gene expression in migration-related genes influencing physiological, morphological, and behavioral traits. Moreover, that Hale et al. (2016) found all of these genes were upregulated in migratory smolts compared to residents in the Sashin Creek population points towards these genes having a key involvement in the decision to migrate. Therefore, changes in the genome that cause a gene to be differentially expressed might not be linked to mutations in the differentially expressed gene.

The next step for this project is to determine the location of two genes, *Opsin SWS1* and *11-cis Retinol Dehydrogenase,* in the linkage map. In addition, more phototransduction genes SNP should be identified to see the location of more vision and photosensory genes in the *O. mykiss* genome. By including more genes, evidence for phototransduction location relative to migratory-related QTLs can be better understood.

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