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Invited Review

Effects of Crossovers Between Homeologs on Inheritance and Population Genomics in Polyploid-Derived Salmonid Fishes

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Abstract

A whole genome duplication occurred in the ancestor of all salmonid fishes some 50–100 million years ago. Early inheritance studies with allozymes indicated that loci in the salmonid genome are inherited disomically in females. However, some pairs of duplicated loci showed patterns of inheritance in males indicating pairing and recombination between homeologous chromosomes. Nearly 20% of loci in the salmonid genome are duplicated and share the same alleles (isoloci), apparently due to homeologous recombination. Half-tetrad analysis revealed that isoloci tend to be telomeric. These results suggested that residual tetrasomic inheritance of isoloci results from homeologous recombination near chromosome ends and that continued disomic inheritance resulted from homologous pairing of centromeric regions. Many current genetic maps of salmonids are based on single nucleotide polymorphisms and microsatellites that are no longer duplicated. Therefore, long sections of chromosomes on these maps are poorly represented, especially telomeric regions. In addition, preferential multivalent pairing of homeologs from the same species in F_1 hybrids results in an excess of nonparental gametes (so-called pseudolinkage). We consider how not including duplicated loci has affected our understanding of population and evolutionary genetics of salmonids, and we discuss how incorporating these loci will benefit our understanding of population genomics.

Subject areas: Genomics and gene mapping

Key words: homeologs, interference, ohnologs, pseudolinkage, residual tetrasomy, Salmonidae

Introduction

An apparent autopolyploid whole genome duplication event occurred in an ancestor of all salmonid fishes (salmon, trout, char, whitefish, and grayling) some 50–100 million years ago (Ohno et al. 1968; Allendorf and Thorgaard 1984; Macqueen and Johnston 2014). Ohno (1970) used 4 major lines of support for this conclusion. Salmonids have about twice as much DNA per cell as closely related fish, and they typically have about 100 chromosome arms, about twice as many as closely related fish. Multivalent chromosome pairing has been observed in meiotic preparations (Davisson et al. 1973). Finally, early work with allozymes indicated a higher proportion of duplicated loci in salmonids than in other fishes. We have included a Glossary because many of the

terms have been either not commonly used or have been misused. Words included in the Glossary are bolded the first time that they appear in the text.

More recently, the conclusion of a polyploidy ancestry for salmonids has been supported by genomic analysis. Koop et al. (2008) obtained expressed sequence tags from 6 salmonid species and the northern pike (*Esox lucius*). The salmonids, pike, and smelt comprise the basal teleost superorder Protacanthopterygii (Nelson 2006). Koop et al. (2008) concluded that the salmonid transcriptome revealed a complex history of gene duplication that is consistent with an ancestral polyploid event. Macqueen and Johnston (2014) described an extensive set of gene paralogs retained in all 3 major lineages of salmonids (subfamilies Salmoninae, Thymallinae, and Coregoninae) consistent with a polyploid ancestry.

There has been a resurgence of interest in the role of polyploidy in evolution because of the ability to use genomic approaches to understand the evolution of polyploids (Adams and Wendel 2004; Pennisi 2012; Madlung 2013). In addition, several papers have explored the possible evolutionary advantages of polyploidy (Comai 2005; Soltis and Burleigh 2009). Polyploidy is much more common in plants than animals (Mable 2004), but polyploidy has also occurred in amphibians and fish (Mable et al. 2011). In general, polyploidization has played an important role in the evolution of nearly every group of organisms. Therefore, understanding the effects of polyploidy in salmonid fishes is of great general interest.

Early inheritance studies with salmonids revealed a variety of unusual patterns of inheritance (e.g., partial or **residual tetrasomy** and so-called **pseudolinkage**) of duplicated loci (reviewed in Wright et al. 1983 and Allendorf and Danzmann 1997). Recent papers describing the population genomics of Pacific salmon species (*Oncorhynchus* spp.) have tended to ignore their polyploid genome and have not recognized possible complications because of their unusual transmission genetics (Hecht et al. 2012; Hohenlohe et al. 2013; Narum et al. 2013). Likewise, most contemporary maps of the salmonid genome are constructed only after removal of loci of **paralogous** origin (Everett et al. 2012; Miller et al. 2012; Gagnaire et al. 2013a), which limits alignment of **homeologs** and reduces the map resolution in telomeric regions where homeologs are concentrated. In contrast, studies of Atlantic salmon (*Salmo salar*), for which extensive map and DNA sequence resources exist (Davidson et al. 2010; Lien et al. 2011), routinely incorporate awareness of homeologous chromosomes in population studies (Brenna-Hansen et al. 2012; Bourret et al. 2013) and mapping studies (Gidskehaug et al. 2011; Lien et al. 2011).

The overall purpose of this review is 1) to synthesize what is known about the transmission genetics of salmonid fishes and 2) to consider how ignoring these patterns could lead to erroneous conclusions about their genomic organization and population genetics.

Chromosome Pairing in Tetraploids

The meiotic pairing of the 4 chromosomes in tetraploids is much more complex than pairs of chromosomes in diploids because **preferential chromosome pairing** often occurs and can produce a variety of different segregation ratios (Little 1945). At one extreme in recent **autotetraploids**, we expect random chromosome pairing that results in tetrasomic ratios. At the other extreme in **allotetraploids** derived from species with highly divergent genomes, we expect complete preferential pairing between conspecific chromosomes that results in diploid inheritance. However, partial preferential pairing can result in an assortment of segregation ratios. Preferential pairing has been shown to occur in a variety of tetraploid plant species (Lentz et al. 1983). For example, Benavente and Orellana (1989) found that identical chromosomes were more likely to pair with each other during meiosis than similar but not identical chromosomes in autotetraploid rye (*Secale cereal*). Based on these and other results, these authors concluded that sequence divergence among chromosomes plays an important role in preferential pairing behavior of chromosomes in polyploids.

More recent studies with the yellow cress plant (*Rorippa* spp.) report inheritance ratios in interspecific hybrids that are intermediate to disomic and tetrasomic inheritance (Stift et al. 2008). These authors conclude that chromosomes pair preferentially in meiosis with the **homolog** from the same parental species. They discuss the implications of inheritance intermediate to disomic and tetrasomic for linkage mapping and population genetics. Stift et al. (2008) present a likelihood-based approach that models preferential pairing to understand tetrasomic inheritance. They also demonstrate that methods that have been developed for either disomic or tetrasomic tetraploids may not be generally applicable, particularly in systems where hybridization is common.

Danzmann and Bogart (1982) reported a polymorphism for segregation ratios in the autotetraploid gray tree frog (*Hyla versicolor*). Some individuals produced segregation ratios that were disomic, some produced segregation ratios that were tetrasomic, and some produced segregation ratios that were intermediate. These authors suggest that these differences in segregation ratios resulted from differences in preferential pairing among the 4 chromosomes.

Inheritance Studies

The first inheritance studies in salmonid fishes used the then newly developed technique of enzyme electrophoresis (Morrison and Wright 1966). Allozyme studies suggested that approximately 65% of the enzyme loci in the salmonid genome retain duplicate gene function (Allendorf and Thorgaard 1984). Some of these **ohnologs** demonstrate divergence in both structure and expression. For example, *LDH-B1* and *LDH-B2* show extremely different patterns of tissue-specific expression for the enzyme lactate dehydrogenase (Allendorf et al. 1984). These differences in expression are ancient because they are shared by both the subfamilies Thymallinae and Salmoninae (Allendorf and Thorgaard 1984). Thus, the evolution of these tissue-specific patterns of expression predated the divergence of these 2 subfamilies some 30–40 million years ago (Macqueen and Johnston 2014). However, other ohnologs show no evidence of divergence and still share the same alleles (e.g., *MDH-B1* and *MDH-B2*); pairs of loci that share alleles have been referred to as **isoloci** (Allendorf and Thorgaard 1984).

Tetrasomic Inheritance

Inheritance studies with salmonids using allozyme loci indicated that most loci in the salmonid genome are inherited disomically (Allendorf and Utter 1973; Allendorf and Thorgaard 1984). That is, these loci have become rediploidized. However, some pairs of duplicated loci have shown patterns of inheritance that can be explained only by pairing and crossovers between homeologous chromosomes. For example, the 2 loci (*MDH-B1* and *MDH-B2*) resulting from the duplication of the vertebrate *MDH-B* gene exhibit residual tetrasomic inheritance (sensu May et al. 1979) in rainbow trout (*Oncorhynchus mykiss*) (Table 1; May et al. 1982; Allendorf and Danzmann 1997). This residual tetrasomic inheritance apparently results from crossovers between homeologs near the end of chromosomes (Figure 1).

Table 1. Residual tetrasomic inheritance in males but not females at the *MDH-B1* and *MDH-B2* loci of rainbow trout (data from Allendorf and Danzmann 1997)

Family	Parental genotypes		Progeny genotypes			Θ
	Female	Male	*BB/BB*	*BB/Bb*	*BB/bb*	
H13	*BB/bb*	*BB/BB*	0	44	0	
				(44)		
			[7]	[29]	[7]	0
H17	*BB/bb*	*BB/BB*	0	249	0	
				(249)		
			[42]	[166]	[42]	0
J31	*BB/bb*	*BB/BB*	0	53	0	
				(53)		
			[9]	[35]	[9]	0
H06	*BB/BB*	*BB/bb*	14	266	9	
				(289)		
			[44]	[177]	[44]	0.242
H18	*BB/BB*	*BB/bb*	12	183	5	
				(200)		
			[33]	[133]	[33]	0.255
K37	*BB/BB*	*BB/bb*	5	259	7	
				(271)		
			[45]	[181]	[45]	0.133

Expected numbers of progeny with disomic inheritance in parentheses and with tetrasomic inheritance in brackets. θ, proportion of tetrasomic inheritance.

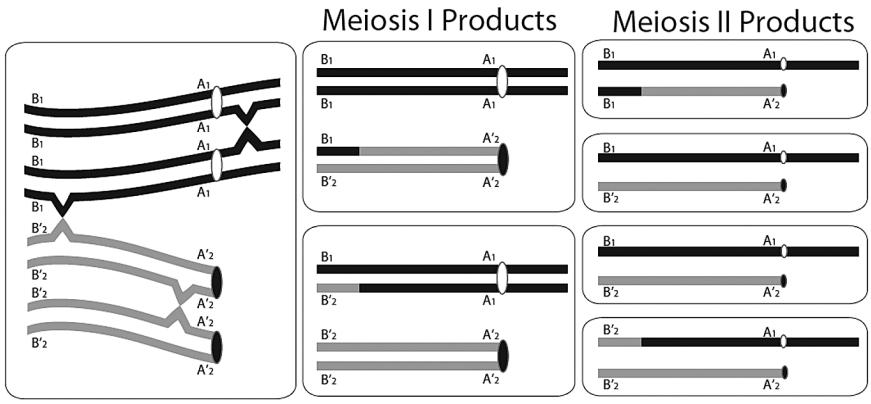

Figure 1. Model of partial tetrasomic inheritance resulting from homeologous crossovers. Crossovers between homeologs will produce intermediate disomic–tetrasomic segregation ratios for more distal loci (B_1 and B_2), whereas loci (A_1 and A_2) near the centromere will show disomic inheritance. Homeologs will pair with each other only in telomeric regions that retain sequence similarity. It is assumed that chromatids that crossover go to opposite poles. A_1 and A_2 represent ohnologs that are located near their centromeres (e.g., *LDH-B1* and *LDH-B2*). B_1 and B_2 represent ohnologs that remain isoloci (e.g., *MDH-B1* and *MDH-B2*).

In salmonids, tetrasomic inheritance has been found primarily in males; females from these same populations transmit these same loci disomically (Table 1). Cytological analysis is in agreement with these observations, as **multivalent** pairings during meiosis have been found primarily in males (Davisson et al. 1973; Timusk et al. 2011). In addition, differences exist between intraspecific populations. For example, there is no evidence of residual tetrasomic inheritance in males from some populations of rainbow trout (Allendorf and Danzmann 1997).

Even a very small amount of homeologous recombination will act to maintain the same alleles at the 2 duplicated loci (Figure 2; Allendorf and Danzmann 1997; Meirmans and Van Tienderen 2013). The 2 *MDH-B* ohnologs are analogous to a single locus in 2 populations, with homeologous exchanges acting analogously to gene flow between populations. Wright (1931) has shown that a single "migrant" per generation is sufficient to ensure that the same neutral alleles will be shared by populations over long periods of evolutionary time. This does not mean that allele frequencies will be similar in all populations, but rather that these alleles will be found at both loci so that the loci will remain isoloci.

Pseudolinkage

Some pairs of duplicated loci (e.g., *LDH-B1* and *LDH-B2*) demonstrated a pattern of disomic transmission primarily from males in which the **nonparental** (recombinant) gametes are in excess relative to the **parental** gametes (Table 2; Morrison 1970). Pseudolinkage was first observed in interspecific hybrids and is thought to result from the preferential secondary pairing of homeologs from the same species followed by **alternate disjunction** (Figure 3).

Ostberg et al. (2013) found evidence for both residual tetrasomic inheritance and excess of nonparental gametes produced by first-generation hybrids between rainbow trout and Yellowstone cutthroat trout (*Oncorhynchus clarkii bouvieri*). All 8 pairs of homeologous chromosomes previously reported in rainbow trout (Phillips et al. 2006)

displayed rates of recombination greater than 80% in males (Ostberg C, personal communication). Thus, pseudolinkage appears to be a general phenomenon for homeologous chromosome pairs. Ostberg et al. (2013) also reported pseudolinkage in a single pair of homeologs from 1 of 2 females tested (Ostberg C, personal communication).

Pseudolinkage in interspecific hybrids apparently results from preferential pairing of conspecific homeologs because of their greater sequence similarity than homeologs from different species (Figure 3). Similar patterns of preferential pairing between conspecific homeologs in intraspecific hybrids have been described in polyploid ferns (*Ceratopteris thalictroides*; Hickok 1978). Tetrasomic inheritance seems to be more common in populations that have experienced intraspecific hybridization events. For example, the population exhibiting tetrasomic inheritance at *MDH-B1 and MDH-B2* in Allendorf and Danzmann (1997) had a hybrid origin (Leary et al. 1983). Another population of rainbow trout derived from a single source population did not exhibit tetrasomic inheritance at these loci (Allendorf and Thorgaard 1984).

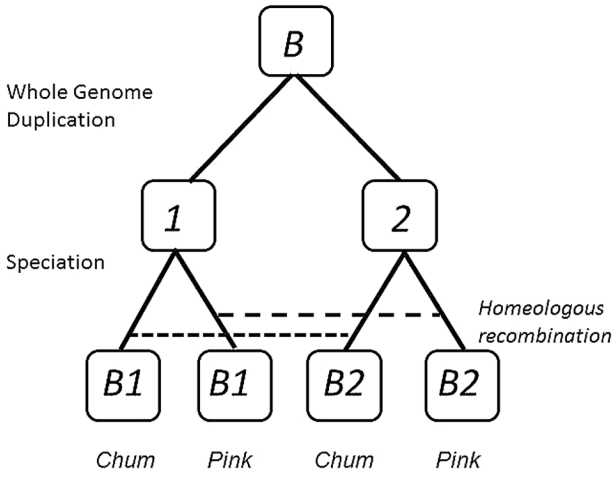

Figure 2. Evolution of isoloci. *B1* and *B2* are the 2 ohnologs produced by the salmonid tetraploid event. *B1* and *B2* are the **orthologous** genes after a speciation event. The broken horizontal lines indicate homeologous recombination events that act to maintain the same alleles at both loci within a species. Therefore, the 2 isoloci within a species will be more similar in sequence to each other than the same isolocus between the 2 species. That is, *MDH-B1* and *MDH-B2* within pink salmon (*Oncorhynchus gorbuscha*) will be more similar to each other than *MDH-B1* and *MDH-B1* between pink and chum salmon (*O. keta*).

There has been some confusion in the literature about the distinction between residual tetrasomy and pseudolinkage. Both involve crossovers between homeologous chromosomes. However, pseudolinkage requires the preferential pairing of conspecific homeologs before they cross over and affects the entire chromosome (Figure 3). Residual tetrasomy does not require preferential pairing of homeologs and only affects loci distal to the homeologous crossover (Figure 1).

Our model of residual tetrasomic inheritance is similar to that of Wright et al. (1983) in that homeologous recombination may make homologous recombination unnecessary as long as resulting chiasmata support formation of the metaphase plate and equational division. Homolog recognition initiates at the telomeres, and pairing continues through the subtelomeric structures toward the centromere (Calderón et al. 2014). If the telomeric sequences of the homeologous sets of chromosomes are undiverged, then either homologous or homeologous recombination can take place first. If pairing of the undiverged sequences is random, then this model would predict that homeologous pairing would be twice as frequent as homologous. Figure 1 shows one of several possible chiasmata formations where this model would support equational division.

Our model of pseudolinkage differs from Wright et al. (1983) in that Wright et al. (1983) propose that homeologous crossovers preclude crossovers between homologs. Thus, in their model, meiosis is achiasmatic in 1 pair of homologs because there are no homologous crossovers. The high frequency of recombinant genotypes reported by Ostberg et al. (2013; personal communication) in F_1 interspecific hybrids would suggest that under the Wright et al. (1983) model, 1 pair of homologs rarely cross over during meiosis. Our model includes both homologous and homeologous crossovers occurring in the same meiotic event. Our model and Wright et al. (1983) model make different predictions that can be tested with future data from appropriate crosses.

Chromosomal Basis

Early studies of duplicate loci in salmonids by J. E. Wright and colleagues (Wright et al. 1980; Lee and Wright 1981; Wright et al.

Table 2. Pseudolinkage (excess of nonparental gametes) in only male first-generation hybrids between brook trout (A_1A_1/A_2A_2) and lake trout ($A'_1A'_1/A'_2A'_2$) (data from Morrison 1970)

Family	Parental genotypes		Progeny genotypes				r^a
	Female	Male	$A_1A_1\ A_2A_2$	$A_1A_1\ A_2A'_2$	$A_1A'_1\ A_2A_2$	$A_1A'_1\ A_2A'_2$	
N109	$A_1A'_1/A_2A'_2$	A_1A_1/A_2A_2	40	33	34	33	0.48
			(35)	(35)	(35)	(35)	
N112	$A_1A'_1/A_2A'_2$	A_1A_1/A_2A_2	18	12	24	18	0.50
			(18)	(18)	(18)	(18)	
N113	$A_1A'_1/A_2A'_2$	A_1A_1/A_2A_2	28	21	40	32	0.46
			(28)	(28)	(28)	(28)	
N116	A_1A_1/A_2A_2	$A_1A'_1/A_2A'_2$	12	36	34	13	0.74***
			(24)	(24)	(24)	(24)	
N120	A_1A_1/A_2A_2	$A_1A'_1/A_2A'_2$	4	24	37	7	0.85***
			(18)	(18)	(18)	(18)	
N124	A_1A_1/A_2A_2	$A_1A'_1/A_2A'_2$	26	81	93	19	0.81***
			(55)	(55)	(55)	(55)	

Expected number of progeny with independent assortment in parentheses.
[a]r recombination rate (proportion of recombinant genotypes).
***$P < 0.001$.

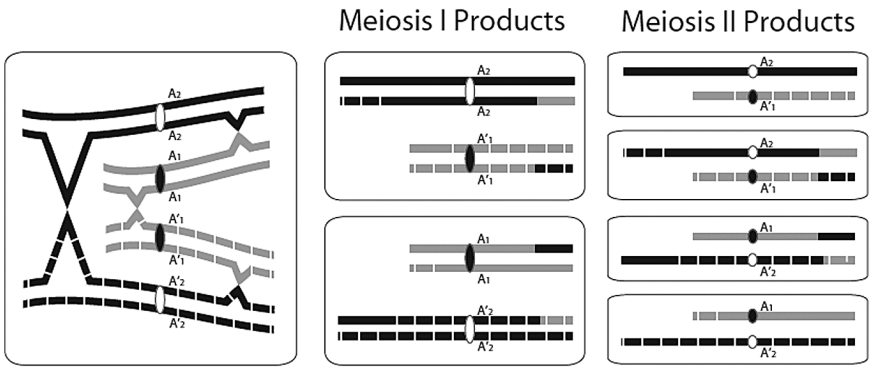

Figure 3. Model of pseudolinkage resulting from homeologous crossovers and preferential pairing of homeologs from the same taxon (population or species). The A_1 and A_2 loci represent ohnologs that are located near their centromeres (e.g., *LDH-B1* and *LDH-B2*). The A_1 and A_2 alleles come from 1 taxon and the A'_1 and A'_2 alleles come from the other taxon. The dashes indicate chromosomes originating in the same taxon as the A'_1 and A'_2 alleles. It is assumed that chromatids that crossover go to opposite poles. Loci telomeric to the homeologous crossovers will show partial tetrasomic inheritance as in Figure 1. In hybrids, preferential pairing of homeologs from the same species (or population) because of greater sequence similarity will result in all gametes being recombinants (i.e., A_1 and A'_2 or A'_1 and A_2), resulting in an overall tendency for a deficit of parental gametes (i.e., pseudolinkage). The crossover event between the top and bottom chromosomes occurs between apparently distant arms because we are representing a 3-dimensional process in 2-dimensions.

1983) were based on both cytological and segregation studies. They provided evidence for homeologous pairing of particular chromosomes, and their studies have contributed significantly to our current understanding of residual tetrasomic inheritance. They observed that homeologous pairings appear as occasional tetravalent rods and rings at metaphase I in male meiosis resulting in tetrasomic inheritance. The Wright model is based on homeologous pairing of centrically fused metacentric chromosomes formed through Robertsonian translocations; inherent in their model is that a metacentric is always involved in multivalent pairing. The model assumes that the metacentrics were derived from fusions of originally nonhomologous acrocentrics and that 2 acrocentrics can pair tetravalently with the homeologous arm of the metacentric resulting in crossing over between homeologous arms. In species with a preponderance of metacentric chromosomes, multivalent pairing of 4 metacentrics is possible, a result of fusion of nonhomologous acrocentrics with both homeologous acrocentrics (Wright et al. 1983).

Wright et al. (1983) suggested on the basis of allozyme data that there are 4 to 10 homeologous chromosome pairs in salmonids. Eight pairs of homeologous chromosomes have been described in rainbow trout (Phillips et al. 2006), Chinook salmon (Brieuc et al. 2014), Atlantic salmon (Lien et al. 2011), and coho salmon (Kodama et al. 2014).

Recent studies provide additional support for the role of metacentric chromosomes in the maintenance of duplications in salmonids. Phillips et al. (2009) found large conserved syntenic blocks between chromosomes of Atlantic salmon and rainbow trout. They also found that most of the homeologous regions in both species were located on metacentric chromosomes. Recent genomic studies have focused on the distribution of duplicated loci as well as comparative mapping of chromosomal arms among species. Lien et al. (2011), in a linkage map from Atlantic salmon with more than 5000 single nucleotide polymorphisms (SNPs), showed that the majority of duplicated loci were located on 8 pairs of homeologous arms.

Comparative mapping of the Pacific salmon (*Oncorhynchus*) has provided strong evidence for chromosomal rearrangements among the species but also evidence for the conservation of some metacentric and acrocentric chromosomes (Naish et al. 2013; Brieuc et al. 2014; Kodama et al. 2014). Similar to the Atlantic salmon findings, Brieuc et al. (2014) found the majority of the duplicated loci in Chinook salmon (*O. tshawytscha*) were located on a subset of 16 chromosomes arms. They observed a high density of duplicated loci located in distal regions and found that pairings involved at least 1 metacentric chromosome. Brieuc et al. (2014) also observed that many of the homeologous pairs with high numbers of duplicated markers appear conserved within *Oncorhynchus* species, suggesting that retention of conserved homeologous pairing in some arms preceded species divergence within the genus. Following the study of Brieuc et al. (2014), Kodama et al. (2014) developed a linkage map for coho salmon (*O. kisutch*) and presented similar findings. Like the previous studies, they found the majority of the duplicated loci located on 16 linkage groups. They also found that the duplicated regions were conserved across syntenic arms across *Oncorhynchus* species. Eight homeologous arm pairs with a high retention of duplicated loci observed in coho salmon were also observed in Chinook salmon, and 4 homeologous arm pairs were conserved in Atlantic salmon. Kodama et al. (2014) hypothesized that rediploidization in salmon may have been prevented or retarded by the formation of metacentric chromosomes after the whole genome duplication event.

Taken together, these studies suggest that arms associated with some metacentric chromosomes retain duplicates, duplicates are distally located, and at least 1 metacentric chromosome is likely involved in homeologous pairings. Recent results from genomic studies are consistent with the observation of J. E. Wright and colleagues that the involvement of at least 1 metacentric chromosome provides the stability required for the formation of multivalents (Wright et al. 1983).

Development of DNA Markers for Population Genetics and Mapping

A number of research groups began to develop microsatellite markers in salmonids in the early 1990s. Genotypes of duplicated loci are difficult to score because of the presence of 4 gene copies and up to 4 alleles in a single individual. In addition, even if individuals can be correctly genotyped, the population genetic interpretation of duplicated loci is difficult (e.g., estimation of allele frequencies at individual loci; Waples 1988). Therefore, researchers developing

microsatellites tended to avoid using loci that appeared to be duplicated. Although this approach makes intuitive sense, and may not be particularly problematic for general inferences about demographic patterns (e.g., effective population size or migration rates) that require a handful of loci, it has resulted in discarding a significant amount of information from duplicated loci. Doing so could comprise a substantial proportion of the genome, particularly if homeologs that are behaving as isoloci are localized in the genome. For example, Coulibaly et al. (2005) detected 70 microsatellite markers in rainbow trout; half of these were found to be duplicated and were therefore "discarded from the polymorphism survey."

The development of SNP markers in salmonids followed a similar path a decade later. Again, the inability to assign SNP alleles in duplicated genes to respective homeologs invalidated the utility of such loci for studies of population genetics. Smith et al. (2005) used Sanger sequencing of 89 kb in an early SNP discovery effort; 32% of the 5′-nuclease assays that they attempted detected duplicated loci and were eliminated from further study. Efforts to use transcriptome sequencing for SNP discovery had even higher failure rates (Seeb et al. 2011) because of the challenges encountered when attempting to sort expressed sequence tag transcripts into homeologs (especially with short reads; see Everett et al. 2011).

Terms to describe these duplicated genes vary. The term isolocus has been widely used in allozyme studies of salmonids. Genomic studies with salmonids have often used the term **paralogous sequence variation** (**PSV**) for any type of paralogous duplication (inter- and intrachromosomal). However, Gidskehaug et al. (2011) used both the terms PSV as well as **multisite variants** (**MSVs**). See MSV in the Glossary for a discussion of this. Only a few studies with microsatellites have included isoloci (see Lindner et al. 2000) because the genotypes are not easily distinguishable and interpretation is complicated by overlapping banding patterns.

Recombination and Linkage Maps

Inheritance studies with microsatellites and SNPs are in agreement with studies using allozymes. Linkage maps in salmonid fishes using both microsatellite and SNPs have reported both residual tetrasomy and pseudolinkage: rainbow trout (Sakamoto et al. 2000; Guyomard et al. 2006), brown trout *Salmo trutta* (Gharbi et al. 2006), and coho salmon (McClelland and Naish 2008). Recent transmission genetic studies using thousands of SNPs in Atlantic salmon (*S. salar*; Gidskehaug et al. 2011; Lien et al. 2011) and Chinook salmon (Brieuc et al. 2014) are concordant with our understanding of these processes based upon allozyme loci. For example, approximately 20% of all loci in Atlantic salmon are isoloci, and these loci are found near the telomeres (Gidskehaug et al. 2011). Similarly, Allendorf and Thorgaard (1984) found that 24% of 33 enzyme coding loci in rainbow trout were isoloci. Novel approaches to detect and map homeologous markers coupled with genotyping of thousands of loci has confirmed a general telomeric clustering of regions exhibiting tetrasomic inheritance (Lien et al. 2011; Brieuc et al. 2014; Waples et al. 2015).

Mapping studies with **half-tetrad analysis** have shown nearly complete crossover interference for many loci in salmonids. For example, 640 out of 644 half-tetrads for the locus *Sod-1* in rainbow trout were heterozygous (Allendorf et al. 1986). This means that there is exactly 1 crossover in more than 99% of all meiotic events for this locus. Nearly 40% of 34 microsatellite loci showed almost complete interference, and this is likely an underestimate because of the tendency to not include duplicated loci (Lindner et al. 2000). Recent genotyping-by-sequencing (GBS) studies in sockeye salmon (*O. nerka*) support the occurrence of strong interference along most chromosomes (Limborg M, unpublished data).

Half-tetrad analysis has also confirmed the expectation of the model of homeologous recombination (Figure 1) that isoloci are telomeric, far from their centromere. Half-tetrad analysis has been used for **gene-centromere mapping** in salmonids by recovering 2 of the 4 strands (half-tetrads) from a single meiosis. This can be done by fertilizing eggs with sperm that have been genetically sterilized with ultraviolet light, followed by a heat-shock of the eggs 10 min after fertilization to induce retention of the second polar body (Thorgaard et al. 1983). Results support that isoloci tend to be telomeric, with a long map distance from their centromeres (Thorgaard et al. 1983; Allendorf et al. 1986; Seeb and Seeb 1986; Lindner et al. 2000; Brieuc et al. 2014). In contrast, those pairs of duplicated loci showing substantial divergence (e.g., *LDH-B1* and *LDH-B2*) tend to map near their centromeres (Allendorf et al. 1986).

Patterns of recombination in other vertebrates are similar to those seen in salmonid fishes. Overall, there is greater recombination in females than in males (Kong et al. 2002; Dumont and Payseur 2011). In addition, males generally have greater rates of recombination than females toward the telomeres. This difference is based upon both inheritance (e.g., Kong et al. 2002) and cytological studies (Kochakpour and Moens 2008). This seems especially relevant to the observation in salmonids that crossovers between homeologs have been observed only in males and that these crossovers are telomeric.

Based upon estimates in mice, it has been proposed that the lower overall rates of recombination observed in males is caused by greater interference than in females (Petkov et al. 2007). On the surface, this observation seems to be in disagreement with the observed strong interference in female salmonids based on half-tetrad analysis. Unfortunately, there are little data available on the strength of crossover interference based on Mendelian crosses in salmonid or other fishes.

Potential Consequences

The post-polyploid evolution of the genome of salmonid fishes demonstrates non-Mendelian patterns of inheritance because of pairing and recombination between homeologous chromosomes. These unusual patterns of inheritance have been largely ignored in much of the literature describing the population genetics of salmonid fishes. In addition, current genetic maps in most salmonids are based on SNP and microsatellite loci that no longer are duplicated because markers were preferentially retained that exhibited disomic inheritance. Therefore, long sections of chromosomes, especially telomeric regions, might be poorly represented on these maps (Gidskehaug et al. 2011; Brieuc et al. 2014). In this section, we consider possible consequences of this phenomenon.

Hybridization

The issues presented here are likely to be especially important with hybrid populations because of the preferential pairing of intraspecific homeologs. The available evidence suggests that pairing between homeologs is more common in hybrids (Wright et al. 1980; Allendorf and Danzmann 1997; Ostberg et al. 2013). Both inter- and intraspecific hybrids are increasingly common in salmonids because of hatchery releases, stock transfers, etc. Therefore, current practices that exclude duplicated markers to estimate the proportion of admixture in hybrid populations are justified, advisable, and avoid problems associated with non-Mendelian proportions produced by partial tetrasomy and pseudolinkage.

The observed greater rates of homeologous recombination in hybrids would be a source of increased genetic variation. For example, intraspecific hybridization in polyploid ferns has been found to generate new genotypic combinations and release the variability stored within the duplicated loci through homeologous pairing and recombination (Hickok 1978). Thus, perhaps the increase in additive genetic variation caused by homeologous recombination could contribute to the widespread success of many salmonid hybrids (Taylor 2004).

Parentage Assignment

Crossovers between homeologs will produce non-Mendelian segregation ratios in loci distal to the crossover. Molecular markers have been routinely used to identify related individuals within populations assuming Mendelian inheritance (Hill and Weir 2011). A variety of approaches are available to identify parentage of individuals that all assume Mendelian inheritance (Harrison et al. 2013). The possible non-Mendelian inheritance of some markers in salmonids caused by residual tetrasomy would present difficulties. This could be especially problematic in hybrid populations where homeologous exchanges are more likely (e.g., Muhlfeld et al. 2009). Therefore, it is advisable to not use duplicated markers when assigning parentage populations to avoid problems associated with non-Mendelian proportions.

Coalescent Analysis

The coalescent is a powerful approach for connecting a range of demographic and evolutionary processes to patterns of genetic variation in SNP or DNA sequence data (Kingman 2000). Coalescent theory focuses retrospectively on the ancestral relatedness of samples of alleles or haplotypes within and among populations (Wakeley 2009). Unlike phylogenetics, the goal of coalescent theory is usually not to estimate the specific relationships among a sample of sequences. Rather, coalescent theory provides a rigorous model linking evolutionary processes (mutation, migration, genetic drift, and natural selection) to expected patterns of resultant genetic variation.

A particularly useful aspect of the coalescent is the clear relationship between parameters describing the branching pattern of a collected set of haplotypes, such as the time to most recent common ancestor (TMRCA) of all sequences, and evolutionary parameters such as effective population size, migration rate, or strength of natural selection. However, much of this theory has been developed assuming consistent disomic inheritance across the genome. The occurrence of recombination between homeologs will affect the segregation of multiple haplotypes at isoloci, and the resultant coalescent patterns. Importantly, the coalescent patterns may significantly vary across the genomes if recombination between homeologs is isolated to genomic regions such as some telomeres.

In salmonids, the coalescent topology and TMRCA for disomically inherited loci will be most influenced by effective population size and may be quite recent. In contrast, the TMRCA for isoloci will be much deeper and reflect the greater effective population size of isoloci, as well as the time to the divergence among loci from the whole genome duplication (Figure 4). In this way, isoloci resemble so-called "structured coalescent models" of gene flow among 2 or more populations, where the presence of divergent alleles among the populations creates a deeper coalescent pattern. Interestingly, this similarity points to an opportunity for using statistical approaches for the structured coalescent for discovery of recombination between homeologs. Just as significantly deeper coalescence times in the structured coalescent can indicate genomically localized gene flow among populations (Nordborg 1997), significantly greater TMRCA in specific genomic locations in polyploids, such as salmonids, could be used to discover and confirm the presence of isoloci experiencing even infrequent recombination between homeologs.

Runs of Homozygosity

Runs of homozygosity are continuous regions of the genome of individuals that are characterized by the absence of heterozygosity. These regions provide the potential to detect and understand the effects of inbreeding in natural populations that has not been previously possible (Kirin et al. 2010). The distribution of such runs of homozygosity can be used to determine the proportion of the genome identical by descent to estimate individual inbreeding coefficients. In addition, the lengths of such runs can be used to estimate how recent the common ancestors of an individual's parents lived (Kirin et al. 2010). The more generations between an individual and its parents' common ancestor, the shorter the runs will be. Similarly, recent statistical approaches for identifying signatures of selection using haplotype homozygosity (e.g., Voight et al. 2006) could be positively misleading if isoloci are removed from analyses.

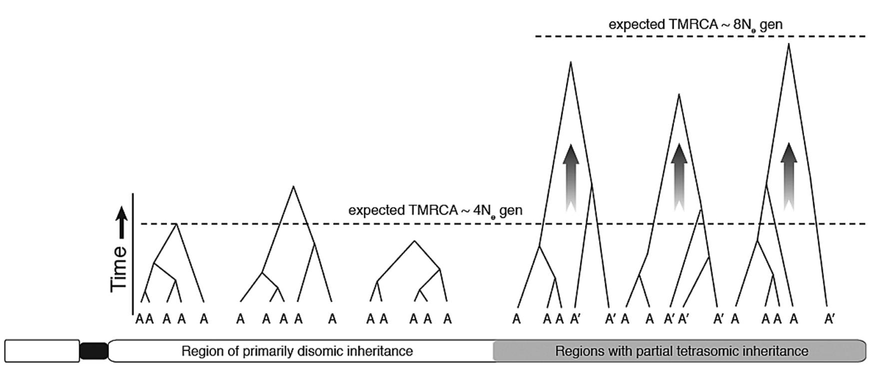

Figure 4. Representation of variation in TMRCA along a chromosome with homeologous recombination of telomeric loci. For loci near the centromere that do not experience homeologous recombination, and therefore segregate disomically, the distribution of coalescence patterns will vary according to the population size with an expected neutral TMRCA of approximately $4N_e$ generations. This is due to the creation and loss of new haplotypes from the processes of mutation and genetic drift occurring at this single locus. For loci that have partial tetrasomic inheritance resulting in the maintenance of haplotypes of both loci (represented by *A* and *A*′ for haplotypes from the 2 loci), the TMRCA of alleles is expected to be approximately $8N_e$ because very little exchange will ensure that the same neutral alleles will be shared by populations over long periods of evolutionary time (Wright 1931).

Homeologous recombination will affect such runs of homozygosity in ways that are difficult to predict. For example, homeologous crossovers can generate apparent runs of homozygosity even in the absence of inbreeding. The exchange of the distal segments of homeologs can result in chromatids with identical distal sections going to the same pole during meiosis (see Figure 1). These segments will be identical by descent even though they are on different chromosomes.

Telomeres Gone Missing

The exclusion of isoloci, which tend to be telomeric, from mapping and population studies using GBS causes a bias that may misinform some interpretations. Many current genetic maps and genome scans currently filter isoloci (e.g., Hecht et al. 2012; Miller et al. 2012; Bourret et al. 2013; Gagnaire et al. 2013a, 2013b; Everett and Seeb 2014; Palti et al. 2014). Studies of salmonids that map in both sexes often find elevated recombination rates in females (female/male ratios routinely as high as 2:1; e.g., Gharbi et al. 2006; Rexroad et al. 2008; Naish et al. 2013). This elevated ratio is presumably because recombination in telomeric regions was poorly characterized in males.

In an extreme example, Moen et al. (2004) found the female/male recombination ratio to be 8.26:1 in maps of Atlantic salmon that did not include isoloci. Lien et al. (2011) suggested that their more even recombination rate between the sexes (1.38:1) resulted from the inclusion of telomeric regions.

In humans, subtelomeric regions are known to be complex, dynamic, and variable regions that harbor adaptively important gene families (Mefford et al. 2001; Mefford and Trask 2002). Morgan et al. (2013) demonstrated the adaptive importance of numerous telomere-associated genes. Studies that exclude isoloci may therefore be missing important regions of adaptation.

Summary

Homeologous recombination is an important factor in the evolution and reshaping of genomes following polyploid events. Homeologous recombination will result in inheritance ratios intermediate between those expected with disomic and tetrasomic inheritance (Gaeta and Pires 2010). Understanding the genomic effects of partial tetrasomic inheritance and preferential pairing of homeologous chromosomes with similar sequences is crucial for applying current genomic approaches to understand the evolution of polyploid species such as salmonids, as well as the many polyploid plant species.

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Glossary

Allotetraploid: A tetraploid that is established from hybridization of 2 different species. Allotetraploids carry 4 complete sets of chromosomes, 2 derived from each parental species.

Alternate disjunction: Process in meiosis in which chromosomes that cross over with each other pass to opposite poles.

Autotetraploid: In contrast to an allotetraploid, a polyploid in which both sets of chromosomes are derived from the same species.

Gene-centromere mapping: Mapping of a locus in relation to the centromere using gynogenetic diploid or triploid progeny.

Half-tetrad analysis: Recovering and genotyping 2 meiotic products from a single meiosis.

Homeologous: Partially homologous chromosomes indicating original ancestral homology. In allotetraploids, the 2 sets of chromosomes derived from different species are considered homeologous. Also spelled homoeologous.

Homologous: Genes or chromosomes that contain the same gene composition as each other but that are not usually identical. In a diploid organism, there is 1 maternal and 1 paternal homolog for each chromosome, generally with multiple polymorphisms present between the two.

Isoloci: A pair of loci located on homeologous chromosomes that share alleles because of homeologous exchanges so that alleles cannot be unambiguously assigned to 1 locus or the other.

MSV3/MSV5: Genotype signal from 4 gene copies that are scored on Illumina Infinium BeadArrays. In an MSV3, 1 ohnolog is fixed resulting in genotypes (*AA*, *AA*) (*AB*, *AA*) and (*BB*, *AA*) or alternatively (*AA*, *AA*), (*AA*, *AB*), and (*AA*, *BB*). In an MSV5, both ohnologs are polymorphic for the same 2 alleles resulting in 5 phenotypes (*AAAA*, *AAAB*, *AABB*, *ABBB*, and *BBBB*; Gidskehaug et al. 2011).

Multisite variants (MSVs): From Gidskehaug et al. (2011): "A PSV is created when there is a base pair difference between the sequences of two paralogues, but the substitution does not segregate within either paralogue. Another source of variation in polyploid genomes are multisite variants (MSV) which, in contrast to PSVs, segregate for a base substitution in one or both of the paralogous loci."

Multivalent: The presence of more than 2 chromosomes synapsed in a unit during prophase I of meiosis.

Ohnolog: Originally defined as duplicate genes produced by the process of whole genome duplication named in honor of Susumu Ohno (Wolfe 2000). Also sometimes used to describe the relationship between chromosomes produced by whole genome duplication, just as homeologous is used to describe both the relationship between genes and chromosomes.

Orthologous: Genes in 2 species that are descended from a single gene in a common ancestor of these species.

Paralogous: The homology between 2 genomic segments (paralogs) in the same organism that arose from a duplication event. Includes both inter- and intrachromosomal duplications.

Paralogous Sequence Variation (PSV): Variants with base pair difference between sequences of 2 ohnologs

Parental and Nonparental gametes: Parental gametes are those in which the 2 alleles derived from the same parent are passed on to progeny. For example, assume that a double-heterozygous individual is produced by a mating between *AB*/*AB* and *ab*/*ab* parents. The *AB* and *ab* gametes are parental and the *Ab* and *aB* gametes are nonparental.

Preferential pairing: Pairing of homeologous chromosomes during meiosis in which chromosomes with more similar sequences are more likely to pair with each another.

Pseudolinkage: A process in which preferential pairing of homeologs from the same parental species, or population, produces an excess of nonparental multiple locus gametes produced by F_1 hybrids. This process is much more common in males than in females.

Residual tetrasomy: A process where segregation ratios that are intermediate between those expected with disomic and tetrasomic inheritance are observed as a result of recombination between homeologs.