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Bayesian genome-wide association analysis for body weight in farmed Atlantic salmon (*Salmo salar* L.)

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Summary

We performed a genome-wide association study to detect markers associated with growth traits in Atlantic salmon. The analyzed traits included body weight at tagging (BWT) and body weight at 25 months (BW25M). Genotypes of 4662 animals were imputed from the 50K SNP chip to the 200K SNP chip using FIMPUTE software. The markers were simultaneously modeled using Bayes C to identify genomic regions associated with the traits. We identified windows explaining a maximum of 3.71% and 3.61% of the genetic variance for BWT and BW25M respectively. We found potential candidate genes located within the top ten 1-Mb windows for BWT and BW25M. For instance, the *vitronectin* (*VTN*) gene, which has been previously reported to be associated with cell growth, was found within one of the top ten 1-Mb windows for BWT. In addition, the *WNT1-inducible-signaling pathway protein 3, melanocortin 2 receptor accessory protein 2, myosin light chain kinase, transforming growth factor beta receptor type 3 and myosin light chain 1* genes, which have been reported to be associated with skeletal growth in humans, growth stimulation during the larval stage in zebrafish, body weight in pigs, feed conversion in chickens and growth rate of sheep skeletal muscle respectively, were found within some of the top ten 1-Mb windows for BW25M. These results indicate that growth traits are most likely controlled by many variants with relatively small effects in Atlantic salmon. The genomic regions associated with the traits studied here may provide further insight into the functional regions underlying growth traits in this species.

Keywords Bayes C, growth, imputation, myosin, single nucleotide polymorphism

From an economic perspective, rapid growth is one of the most desirable traits in Atlantic salmon (*Salmo salar*) production. The identification of genetic variants involved in the phenotypic variation of growth-related traits is crucial for understanding the biological factors associated with these traits and the optimal exploitation of them by means of genetic improvement (Yáñez *et al.* 2015). The availability of dense single nucleotide polymorphism (SNP) arrays for Atlantic salmon has made it possible to use genome-wide association studies (GWAS) to identify SNPs associated with economically important traits (Houston *et al.* 2014; Yáñez *et al.* 2016). For instance, GWAS using thousands of markers have recently been conducted to detect markers associated with disease resistance traits (Correa *et al.* 2015, 2016; Tsai *et al.* 2016) and growth (Gutierrez *et al.* 2015; Tsai *et al.* 2015) in Atlantic salmon. Growth-related traits appear to be polygenic in this species, with a high number of loci with small effect controlling the traits (Gutierrez *et al.* 2015; Tsai *et al.* 2015). GWAS can achieve high statistical power to detect variants of small to medium effect size by increasing the number of samples with both phenotypic and genotypic information and increasing the number of genetic markers by imputing genotypes (Marchini & Howie 2010; Hong & Park 2012). Methods modeling all markers simultaneously, such as Bayesian regression models (Fernando & Garrick 2013), are becoming increasingly popular for GWAS and seem to provide better estimates compared to the conventional analysis of modeling each marker individually (Goddard *et al.* 2009). The objective of this study was to perform a Bayesian GWAS for growth traits in a commercial Atlantic

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salmon population using a larger number of samples and a greater resolution of markers compared to previously performed studies (Gutierrez *et al.* 2015; Tsai *et al.* 2015).

The 4662 Atlantic salmon (representing 118 full-sib families) used in the current study belong to the 2010 year-class of the breeding program of Salmones Chaicas (Puerto Montt, Chile) (Yáñez *et al.* 2013, 2014; Correa *et al.* 2015, 2016). The eggs of each full-sib family were incubated and reared in separate tanks from fecundation until tagging. An average number of 39 fish/family (ranging from $n = 17$ to 42) were PIT (Passive Integrated Transponder) tagged and distributed in six different tanks, with an average of 777 fish/tank (ranging from $n = 737$ to 814). Fish were reared until they were an average of 25 months old. Body weight at tagging (BWT) and at 25 months (BW25M) were recorded for each individual fish and averaged 13.2 and 304.7 g respectively.

Imputation of genotypes from the medium density (50K) to the high density (200K) SNP chip was carried out using FIMPUTE v2.2 software (Sargolzaei *et al.* 2014). We used 53 parents (19 sires and 34 dams) from year-class 2006 of the study population. These individuals were part of the Chilean 'Farmed A' salmon population used to validate the 200K Affymetrix Axiom® myDesign Custom SNP Array developed by Yáñez *et al.* (2016). These 53 animals were genotyped with the high density chip and used as the reference group for imputation. The 4662 offspring from year-class 2010 of the study population genotyped with the medium density Affymetrix SNP array were obtained from the 2389 fish used by Correa *et al.* (2015) and Bangera *et al.* (2017) and the 2279 fish used by Correa *et al.* (2016, 2017). These fish were used as the validation set for imputation. The animals used as the reference and validation sets are listed in Table S1. Before imputation and GWAS analysis, genotypes and samples were filtered according to the following exclusion criteria: Hardy-Weinberg disequilibrium (P-value $< 1 \times 10^{-6}$), minor allele frequency (MAF > 0.01 for imputation and MAF > 0.05 for GWAS) and genotyping call rate (>0.95). Filtering of genotypes and samples was performed using R software version 3.2.2 (R Development Core Team, 2015). The whole set of phenotypic and genotypic data employed in the current GWAS can be found in the Figshare public repository (https://figshare.com/s/6ed78d903c368d374bd6).

The Bayes C (Habier *et al.* 2011) analyses were performed using GS3 software (Legarra *et al.* 2010). A total of 300 000 iterations were used in the Gibbs sampling, with a burn-in period of 30 000 cycles during which results were saved every 50 cycles.

Convergence and autocorrelation were assessed by visual inspection of trace plots of the posterior variance components (Figs S1 & S2). The adjusted model can be described, in matrix notation as: $\boldsymbol{y} = Xb + Zu + Pc + \sum_{i=1}^{n} g_i a_i \delta_i + e$, where $\boldsymbol{y}$ is the vector of phenotypic records (BWT or BW25M), X is the incidence matrix of fixed effects, b is the vector of fixed effects (sex and age at tagging for BWT and sex, age and tank for BW25M), Z is the incidence matrix of polygenic effect, u is a random vector of polygenic effects of all individuals in the pedigree, P is the incidence matrix of common environment effect caused by early rearing of full sib-groups in common tanks prior to tagging, c is a random vector of common environment effect, g_i is the vector of the genotypes for the ith SNP for each animal, a_i is the random allele substitution effect of the ith SNP, δ_i is an indicator variable (0, 1) sampled from a binomial distribution with parameters determined such that π has as a value of 0.995 and e is a vector of residual effects. The prior assumption is that SNP effects have independent and identical mixture distributions, whereby each marker has a point mass at zero with probability π and a univariate normal distribution with probability $1 - \pi$ having a null mean and variance σ_a^2, which in turn has a scaled inverse chi-squared prior, with $v_a = 4$ degrees of freedom and scale parameter s_a^2 (Fernando & Garrick 2013). The scale parameter was derived as a function of the assumed known genetic variance of the population based on the average SNP allele frequency and number of SNPs assumed to have nonzero effects (Fernando *et al.* 2007).

The proportion of the genetic variance explained by each window was calculated as the summation of the genetic variance of individual markers within the window, according to the following formula: $Vg_i = \left(\frac{2p_i q_i a_i^2}{\sigma_u^2}\right)$, where p_i and q_i are the allele frequencies for the ith SNP, a_i is the posteriori estimated additive effect of the ith SNP on the phenotype and σ_u^2 is the posteriori Bayesian estimate of the polygenic variance for each phenotype using prior information (Lee *et al.* 2013).

A total of 116 594 markers and 4662 samples passed the filtering criteria. Summary statistics for BWT and BW25M are shown in Table 1. The posterior means for variance components and genomic heritability are presented in Table S2. The genomic heritabilities were 0.41 (SD = 0.06) and 0.50 (SD = 0.05) for BWT and BW25M respectively. These estimates are within the expected range based on previously reported estimates for growth traits at different stages of development in Atlantic salmon (Yáñez *et al.* 2013; Gutierrez *et al.* 2015; Tsai *et al.* 2015).

Table 1 Summary statistics for body weight at tagging (BWT) and at 25 months (BW25M) measured in 4662 Atlantic salmon individuals.

	Mean	SD	Median	Min	Max	Mean age (SD) in days
BWT (g)	13.25	3.35	13.20	4.10	29.30	307 (3)
BW25M (g)	304.72	120.46	290.00	52.00	986.00	764 (13)

SD, standard deviation; Min, minimum; Max, maximum.

Manhattan plots showing the proportion of genetic variance explained by each 1-Mb window per chromosome are reported in Fig. 1 for both traits. A total of 2247 SNP windows with a mean of 52 SNPs per window (ranging from 1 to 128 SNPs) were obtained. The top window for BWT and BWM25 explained 3.71% (chromosome 27) and 3.61% (chromosome 23) of genetic variance respectively. The top 10 windows cumulatively explained 11.3% and 20.3% of the total genetic variance for BWT and BW25M respectively (Table 2).

The top 10 windows did not coincide between BWT and BW25M, providing further evidence that they can be considered different traits ($r_p = 0.17$). Furthermore, we suspect that BWT is strongly affected by yolk sac reserves and BW25M is more influenced by the efficiency in feeding from exogenous food.

The full list of genes located within the top ten 1-Mb windows associated BWT and BW25M is shown in Table S3. Here, we focus the discussion on strong functional candidate genes located within the top ten 1-Mb windows that have been suggested to be involved with growth-related traits in previous studies.

For BWT, a window on chromosome 20 (55–56 Mb) contains the *vitronectin* (*VTN*) gene. The *VTN* gene is known

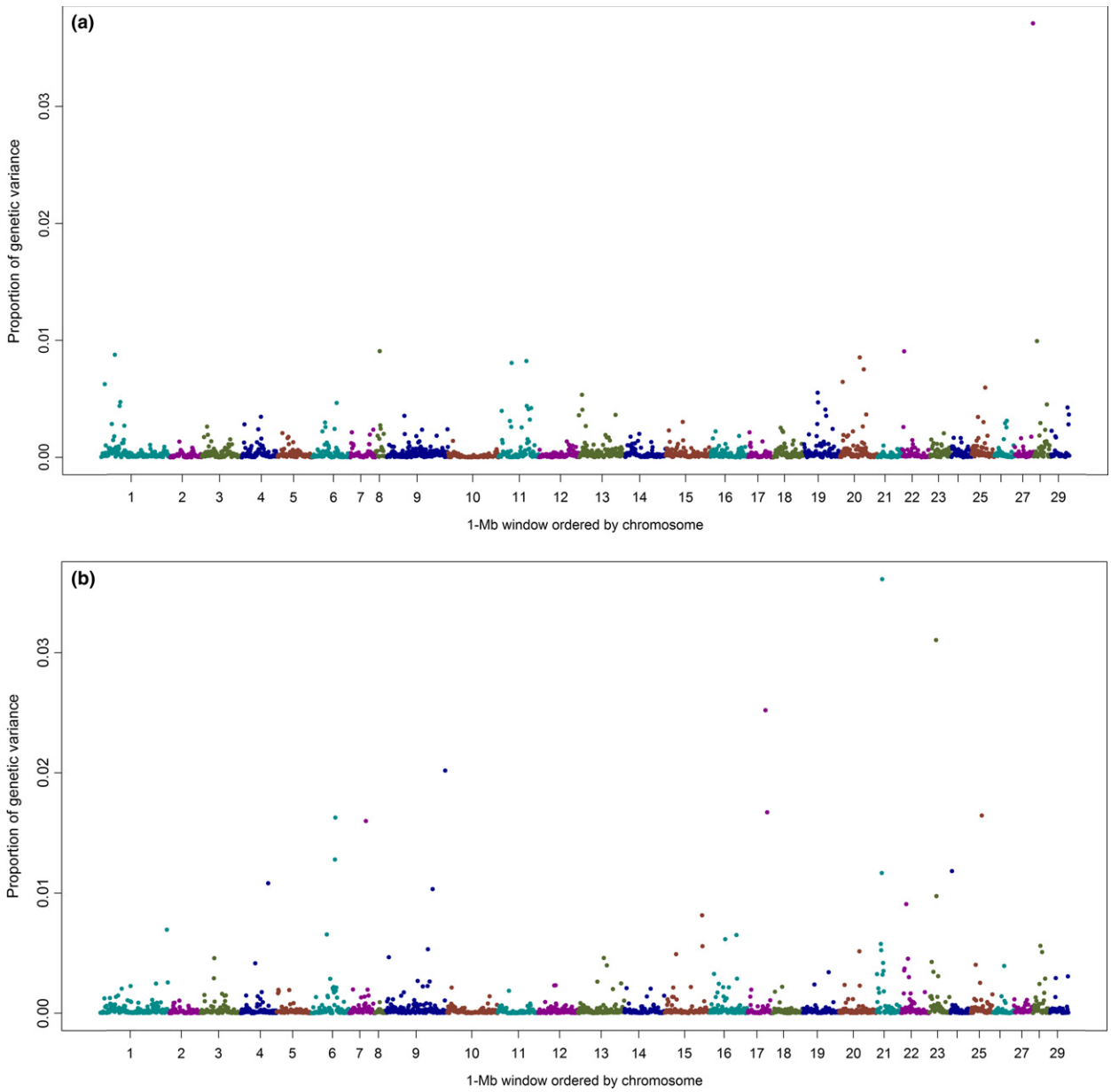

Figure 1 Manhattan plot of genetic variance explained by 1-Mb window for body weight at tagging (a) and body weight at 25 months (b) using Bayes C method.

Table 2 Top 10 ranked 1-Mb windows associated with body weight at tagging (BWT) and at 25 months (BW25M) in Atlantic salmon using Bayes C method.

Chr_Win	SNP/Win	First and last SNP	Map position (bp)	PVar	Genes[1]
BWT					
27_043	038	AQI_UCh-93445434–AQI_UCh-93414721	042 057 193–042 953 237	3.71	*ACOT13, ANGPTL2, CSMD2*
28_008	082	AQI_UCh-93319575–AQI_UCh-93451965	007 090 783–007 973 591	0.99	*A1CF, ASAH2, DKK1*
08_010	072	AQI_UCh-87869829–AQI_UCh-93314978	009 006 835–009 980 098	0.91	*BCL6B, KEN-099, MYNN*
22_005	054	AQI_UCh-93278431–AQI_UCh-93269991	004 091 264–004 999 403	0.91	*DDIT3, DCTN2, ARHGAP15*
01_032	072	AQI_UCh-93333452–AQI_UCh-93309995	031 008 611–031 996 851	0.88	*FAM98B, BDKRB2, CCDC88C*
20_047	093	AQI_UCh-93310786–AQI_UCh-93308483	046 003 709–046 964 042	0.85	MYO1C, *AKAP12, CHP2*
11_065	078	AQI_UCh-93289436–AQI_UCh-93299150	064 007 916–064 967 700	0.82	*ALAD, ANAPC2, APBA2*
11_031	024	AQI_UCh-93339535–AQI_UCh-93272630	030 005 352–030 963 153	0.81	*ACAN, CARTPT,* MYO5A
20_056	058	AQI_UCh-93368110–AQI_UCh-93408751	055 005 320–055 978 019	0.75	*AS3MT, BRIP1,* VTN
20_007	088	AQI_UCh-93315655–AQI_UCh-93405110	006 045 799–006 980 980	0.65	*AP3B2, CCSER1, CDO1*
BW25M					
21_014	067	AQI_UCh-93272835–AQI_UCh-93332308	013 008 474–013 990 167	3.61	FEV, *CRYBA2,* MYLK
23_017	066	AQI_UCh-93334355–AQI_UCh-93276245	016 021 209–016 999 188	3.11	*BRDT, DR1, TGFBR1*
17_042	036	AQI_UCh-93455684–AQI_UCh-87898602	041 009 609–041 981 443	2.52	*CAMK1D, CCDC136, CCDC3*
09_138	050	AQI_UCh-93374705–AQI_UCh-93323972	137 000 990–137 943 730	2.02	*ATG16L1, FUT4,* MRAP2
17_046	097	AQI_UCh-93342711–AQI_UCh-93331774	045 003 027–045 998 046	1.67	*CYB5R3, FGD5, FRRS1*
25_026	039	AQI_UCh-93333802–AQI_UCh-93427207	025 027 279–025 893 133	1.65	*CPS1, ERBB4,* MYL1
06_056	116	AQI_UCh-93434779–AQI_UCh-93304304	055 016 967–055 994 757	1.63	*CD2L6, CTGF, KATNA1*
07_039	052	AQI_UCh-93416832–AQI_UCh-93279966	038 000 310–038 976 001	1.60	*EIF3A, GJB3, HDAC1-B*
06_055	096	AQI_UCh-87930615–AQI_UCh-93411591	054 003 379–054 999 591	1.28	*APZ42, COL5A1,* WISP3
24_004	082	AQI_UCh-93364847–AQI_UCh-93394476	003 002 636–003 960 443	1.18	*CABP7, NF2, PRODH*

Chr_win, chromosome_window; SNP/win, number of SNPs per 1-Mb window; PVar, percentage of variance explained by each 1-Mb window; Genes, summary of the genes located within 1-Mb window (for all genes located in the 1-Mb window, see Table S3).
[1]*Salmo salar* used as reference species.

to participate in immune response and defense (Seiffert 1997), but because the pathways for vitronectin and growth factor signaling are thought to be linked, the interaction of vitronectin with integrins may provide a mechanism for a synergistic action between growth factors and extracellular matrix proteins in promoting cell growth and cell proliferation (Schvartz *et al.* 1999).

For BW25M, windows on chromosomes 6, 9, 21, 23 and 25 contain strong functional candidate genes including the *WNT1 inducible signaling pathway protein 3* (*WISP3* or *CCN6*), *melanocortin 2 receptor accessory protein 2* (*MRAP2*), *myosin light chain kinase* (*MYLK*), *transforming growth factor beta receptor type 3* (*TGFBR3*) and the *myosin light chain 1* (*MYL1*) genes respectively. In humans, the principal role of the *WISP3* gene appears to involve skeletal growth and cartilage homeostasis (Nakamura *et al.* 2009). In dairy cattle, it was suggested that WISP3 is an important regulatory factor involved in the amino acid-mediated regulation of milk protein synthesis and mammary epithelial cell growth (Jiang *et al.* 2015). Sebag *et al.* (2013) suggested that the interaction between *melanocortin-4 receptor* (*MC4R)* and *MRAP2* could stimulate growth during larval development of zebrafish by specifically blocking the action of *MC4R*. The increased expression of *MC4R* in zebrafish embryos causes a decrease in growth and in growth hormone levels and also a compensatory increase in *growth hormone-releasing hormone* (*GHRH*) gene expression (Zhang *et al.* 2012). In mice genetically deficient in *MC4R*, Asai *et al.* (2013) and Liu *et al.* (2013) observed severe obesity. The *MYLK* gene is responsible for smooth muscle contraction and, in neural cells, controls the initiation and growth of astrocytes in culture and participates in transmitter release at synapses formed between cultured sympathetic ganglion cells (Baorto *et al.* 1992). *MYLK* is primarily responsible for regulating phosphorylation of myosin light chain 2 (MLC2) (Warren *et al.* 2012). In a study of pigs, Han *et al.* (2008) observed that individuals containing one specific allele of a SNP marker within *MLC2* had significantly heavier carcass weight (>2.4 kg) and thicker backfat thickness (<1.3 mm) than did those homozygous for the opposite allele, suggesting that *MLC2* is significantly associated with body and carcass traits. In a region within the 1-Mb window located between 16 and 17 Mb on chromosome 23, a predicted gene that encodes for TGFBR3 was found. This binds with three isoforms of TGF-β (TGF-β1, TGF-β2 and TGF-β3) and is responsible for different biological processes such as growth, development, tissue homeostasis, adhesion, apoptosis and regulation of the immune system (Kubiczkova *et al.* 2012; Pardali & Ten Dijke 2012). In a study by Rasal *et al.* (2015), *TGFBR3* showed significant association with the feed conversion rate trait in chickens. Zhang *et al.* (2015) found different expression levels of *MYL1* in the longissimus dorsi muscle between Dorper (fast growing) and Small-tailed Han sheep (slow growing), suggesting that this gene might be related to the growth rate of sheep skeletal muscle. In pigs (Fontanesi *et al.* 2000; Ling *et al.* 2010; Wang *et al.* 2017) and zebrafish (Burguière *et al.* 2011), *MYL1* was reported as

a potential candidate gene for growth and developmental traits.

This study showed that the accuracy of heritabilities increased when using imputed genotypes as compared to the 50K SNP chip (0.34 ± 0.06 and 0.43 ± 0.06 for BWT and BW25M respectively; results not shown). Moreover, imputation improved the ability to discover regions associated with growth traits. For instance, the SNP explaining the highest proportion of genetic variance for BW25M in a previous analysis and within the most significant 1-Mb window for the same trait (AQI_UCh-93440697; results not shown) was an imputed marker that is in a region near the *MYLK* gene, a strong functional candidate gene. Previous studies, using frequentist methods, have shown the polygenic nature of growth-related traits in Atlantic salmon, with no loci surpassing the significance threshold in GWAS (Gutierrez *et al.* 2015; Tsai *et al.* 2015). In the present study, using a Bayesian regression method and a greater number of samples and marker density, we found no evidence of major quantitative trait loci for growth-related traits. The small effect of these loci reinforces evidence of the polygenic nature of these traits. The results presented here identify genomic regions containing strong biological candidates for body weight traits in Atlantic salmon. Further studies, which will be facilitated by the new international initiative FAASG: Functional Annotation of All Salmonid Genomes (Macqueen *et al.* 2017), are required to assess the function of these genes and their effect on growth in Atlantic salmon.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the supporting information tab for this article:

Figure S1 Diagnostic convergence and autocorrelation plot for posterior variances for body weight at tagging (BWT).

Figure S2 Diagnostic convergence and autocorrelation plot for posterior variances for body weight at 25 months (BW25M).

Table S1 Identification, generation, SNP density, group for imputation and the provided reference for the individuals used in the imputation analysis.

Table S2 Posterior means ± standard deviation of variance components explained by 1-Mb windows for body weight at tagging (BWT) and at 25 months (BW25M) in Atlantic salmon.

Table S3 Full list of genes located within top ten 1-Mb windows associated with body weight at tagging (BWT) and at 25 months (BW25M) in Atlantic salmon.