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ORIGINAL ARTICLE

Identification of novel genes significantly affecting growth in catfish through GWAS analysis

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Abstract

Growth is the most important economic trait in aquaculture. Improvements in growth-related traits can enhance production, reduce costs and time to produce market-size fish. Catfish is the major aquaculture species in the United States, accounting for 65% of the US finfish production. However, the genes underlying growth traits in catfish were not well studied. Currently, the majority of the US catfish industry uses hybrid catfish derived from channel catfish female mated with blue catfish male. Interestingly, channel catfish and blue catfish exhibit differences in growth-related traits, and therefore the backcross progenies provide an efficient system for QTL analysis. In this study, we conducted a genome-wide association study for catfish body weight using the 250 K SNP array with 556 backcross progenies generated from backcross of male F1 hybrid (female channel catfish × male blue catfish) with female channel catfish. A genomic region of approximately 1 Mb on linkage group 5 was found to be significantly associated with body weight. In addition, four suggestively associated QTL regions were identified on linkage groups 1, 2, 23 and 24. Most candidate genes in the associated regions are known to be involved in muscle growth and bone development, some of which were reported to be associated with obesity in humans and pigs, suggesting that the functions of these genes may be evolutionarily conserved in controlling growth. Additional fine mapping or functional studies should allow identification of the causal genes for fast growth in catfish, and elucidation of molecular mechanisms of regulation of growth in fish.

Keywords GWAS · QTL · Growth · Fish · Hybrid

Introduction

Growth is an economically important trait in aquaculture because it directly contributes to fish production. Improvements in growth-related traits could reduce time and costs to produce market-size fish. Consequently, the economic significance of growth has prompted continuous studies of its genetic basis. In those studies, genes within the somatotropic axis and transforming growth factor superfamily have been targeted as candidate genes in finfish growth (De-Santis and Jerry 2007). The somatotropic axis, consisting of growth hormone (*GH*), insulin-like growth factors (*IGF-I* and *IGF-II*), growth hormone-releasing hormone (*GHRH*), growth hormone inhibiting hormone (*GHIH* or somatostatin), their associated carrier proteins and receptors, plays a critical role in the metabolic regulation and physiological process (Renaville et al. 2002; De-Santis and Jerry 2007). This axis is responsive to the external environments, such as nutrient intake and culture conditions, and subsequently

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results in the accretion of protein and adipose to be associated with growth rate (De-Santis and Jerry 2007; Richmond et al. 2010). Most of those genes have been demonstrated to be associated with growth enhancement in different fish species (Du et al. 1992; Kang et al. 2002; Tao and Boulding 2003; Wargelius et al. 2005; Hu et al. 2013; Tsai et al. 2014; Feng et al. 2015). Furthermore, there are also other hormones, such as gonadotropin, glucocorticoids and thyroid hormone, involved in modulating the expression of *GH* or *IGF* to indirectly regulate growth (Sternberg and Moav 1999; Wong et al. 2006).

Growth factors and myogenic regulatory factors (MRF) were also widely accepted as growth-modulating genes functioning on myogenesis (De-Santis and Jerry 2007). Myostatin (*MSTN*), also called growth differentiation factor 8 (*GDF-8*), was originally recognized as a negative regulator of skeletal muscle mass in mice and then was found to be associated with growth traits in fish (McPherron and Lee 1997; Sánchez-Ramos et al. 2012; Sun et al. 2016). Moreover, members of MRF, including myogenin, myogenic differentiation (*MyoD*), myogenic factor 5 (*myf5*) and myogenic regulatory factors (*MRF4*), are expressed in skeletal muscle cells and play essential roles in regulating muscle development and growth (Weintraub 1993; Tan and Du 2002; Tan et al. 2006).

In addition to the hormones and peptides within the somatotropic axis and the transforming growth factor superfamily, other genes may also significantly affect growth through other physiological networks modulating energy metabolism and muscle growth. Although it is not practically feasible and cost-effective to detect every single gene and their functions, advances in genetic technologies have facilitated greater level of understanding of genetic variations underlying growth-related traits. Quantitative trait loci (QTL) mapping and genome-wide association studies (GWAS) allowed identification of markers associated with traits of interest. Recently, GWA studies of growth-related traits have been carried out in Atlantic salmon (Gutierrez et al. 2015; Tsai et al. 2015), and several QTL linkage mapping analyses of growth have been conducted in other fish species including orange-spotted grouper (Yu et al. 2016), sea bass (Xia et al. 2013; Wang et al. 2015; Louro et al. 2016), common carp (Laghari et al. 2013, 2014; Lv et al. 2016; Peng et al. 2016), turbot (Robledo et al. 2016), bighead carp (Fu et al. 2016), large yellow croaker (Ye et al. 2014) and tilapia (Liu et al. 2014a). These studies reported a host of candidate genes associated with growth-related traits, whereas not many genes were identified within somatotropic axis and transforming growth factor family (Moghadam et al. 2007; Wang et al. 2008; Wringe et al. 2010; Sánchez-Molano et al. 2011; Liu et al. 2014a; Louro et al. 2016; Peng et al. 2016) (Table S1). Interestingly, quite a few novel genes were considered as candidate genes based on their association with growth traits and their functions related to metabolism and growth (Table S1), demonstrating the complexity of genes involved in growth of fish.

In the United States, catfish is the major aquaculture species, accounting for 65% of the US finfish production in 2008 (FAO 2016). Some growth-related genes have been characterized in channel catfish (*Ictalurus punctatus*) including *IGF-I, GHRH, MSTN* and pituitary adenylate cyclase activating polypeptide (*PACAP*), but in most cases their functional relationships with growth were not demonstrated (McRory et al. 1995; Small and Nonneman 2001; Kocabas et al. 2002; Clay et al. 2005; Small and Peterson 2005). Growth hormone gene was demonstrated to have a positive effect on growth of channel catfish through gene transfer (Dunham et al. 1991; Silverstein et al. 2000), and IGF-II was found to be expressed higher in the fast-growing fish (Peterson et al. 2008). Overall, the genes affecting growth in catfish were not well studied.

GWAS analyses have been successfully conducted in catfish for disease resistance against columnaris disease (Geng et al. 2015), against enteric septicemia of catfish (ESC) (Zhou et al. 2017), heat tolerance (Jin et al. 2016), head size (Geng et al. 2016), body conformation (Geng et al. 2017) and hypoxia tolerance (Wang et al. 2016a; Zhong et al. 2017). Furthermore, our high-density 250K SNP array (Liu et al. 2014b), generated by including SNPs from channel catfish and blue catfish and also interspecific SNPs, has been validated with wild populations and backcross families. At the same time, it was also utilized to genotype three full-sibling channel catfish families (576 fish in total, 192 individuals from each family) to construct the high-resolution genetic linkage map (Li et al. 2014) used in this study. In order to utilize GWAS to identify QTL associated with growth traits in catfish using the high-density 250K SNP array and to scan for candidate genes using the high-quality reference genome sequences (Liu et al. 2016), we have exploited the interspecific hybrid catfish system (Dunham and Masser 2012). Here we report a GWA study using the backcross progeny populations generated from backcross of male F1 hybrid (female channel catfish × male blue catfish) with female channel catfish.

Materials and methods

Ethics statement

All procedures involving the handling and treatment of fish were approved by the Institutional Animal Care and Use Committee (IACUC) at Auburn University prior to the initiation of the experiments.

Experimental fish

A total of 556 1-year-old backcross progenies generated from backcrossing male F1 hybrid catfish (female channel catfish × male blue catfish) with female channel catfish were randomly obtained from Auburn University Fish Genetics Facility. All the female channel catfish were from Marion strain including the female parents of F1 hybrid. The 556 fish were from nine families (Table 1), in which two hybrid males were mated with three and six channel catfish females, respectively. The fish were cultured together, and IBS kinship matrix based on their genotypes was used to assign them to each family (Geng et al. 2015). After 1-year culture, body weight was measured as phenotypic data.

DNA isolation, genotyping and quality control (QC)

Blood sample (0.5–1 mL) was collected in a 1-mL syringe and immediately expelled into a 50-mL tube containing 10 mL of cell lysis solution (Qiagen). To start DNA isolation, 200 µL of blood in cell lysis buffer was combined with 400 µL of fresh cell lysis buffer and 3 µL of fresh proteinase K (20 mg/mL) in the tube. After incubation at 55 °C for 2 h, protein precipitation solution (Qiagen) was added to extract the proteins. DNA was precipitated by cold isopropanol, washed by 70% ethanol and then resuspended in TE buffer (pH 8.0). The integrity of DNA samples was checked by 1% agarose gel electrophoresis stained with ethidium bromide. After quantified by Nanodrop (Thermo Scientific), DNA samples were diluted to 50 ng/µL.

The genotyping was performed using the catfish 250K SNP array (Affymetrix) (Liu et al. 2014b) at GeneSeek (Lincoln, Nebraska, USA). No samples were excluded due to low quality or low call rate (< 0.95). A total of 192,204 SNP markers retained after filtering out SNPs with genotyping error based on Mendelian laws, a call rate < 0.95 or minor allele frequency < 0.05.

Table 1 The pedigree information and phenotypic data of catfish samples in this population

Family ID	Dam	Sire	# of individuals	Body weight (g)
F225_7	Channel 225	Hybrid 7	95	50.8 ± 28.0
F230_7	Channel 230	Hybrid 7	91	68.8 ± 27.0
F213_2	Channel 213	Hybrid 2	55	61.0 ± 21.0
F214_2	Channel 214	Hybrid 2	27	53.2 ± 19.0
F215_2	Channel 215	Hybrid 2	10	36.3 ± 9.0
F221_7	Channel 221	Hybrid 7	106	46.4 ± 18.6
F223_7	Channel 223	Hybrid 7	57	41.7 ± 17.6
F231_7	Channel 231	Hybrid 7	22	38.9 ± 13.5
F220_7	Channel 220	Hybrid 7	93	41.2 ± 18.2
Total			556	

Statistical analysis

Statistical analysis was carried out using the SVS software package (SNP & Variation Suite, version 8.4.4). Linkage disequilibrium (LD) pruning was conducted with a window size of 50 SNPs, a step of 5 SNPs and r^2 threshold of 0.5, generating 7692 independent SNPs and LD blocks for this population. Principal component analysis was conducted using these independent SNP markers. Wright's F_{st} statistics were calculated between each pair of nine families using all the independent SNPs, ranging from 0 (no genetic divergence between families) to 1 (complete isolation from the other families) (Wright 1949; Nei 1973).

To efficiently correct family structure in the association test, Efficient Mixed-Model Association eXpedited (EMMAX) analyses (Kang et al. 2010) in SVS software package using first ten principal components as covariates was conducted for genome-wide association analysis. The model is listed as follows:

$$\mathbf{Y} = \mathbf{Xb} + \mathbf{Zu} + \mathbf{e},$$

where **Y** is the vector of phenotype (body weight); **X** is the matrix of fixed effects including first ten principal components; **b** is the vector representing the coefficients; **Z** is the matrix of random effect; **u** is the coefficient vector, $\mathrm{Var}(\mathbf{u}) = \sigma^2_g G$, where σ^2_g represents the additive genetic variance and G stands for the genomic kinship matrix; **e** is the vector of random residuals.

Manhattan plots of the calculated $-\log_{10}(P \text{ value})$ results for each SNP were generated using SVS software package. Genetic marker map was constructed from channel catfish genetic map (version Coco 1.0) (Liu et al. 2016) due to similar genome architectures of channel catfish and blue catfish (Liu et al. 2003; Kucuktas et al. 2009). Threshold P value for genome-wide significance was calculated based on Bonferroni correction with the estimated number of 7692 independent SNPs and LD blocks (Duggal et al. 2008). Thus, the genome-wide significance threshold was 0.05/7692 = 6.5e−6 ($-\log_{10}(P \text{ value}) = 5.19$). "Suggestive association" allows one false-positive effect in a genome-wide test, indicating the threshold P value was 1/7692 = 1.3e−4 ($-\log_{10}(P \text{ value}) = 3.89$).

Although EMMAX could efficiently correct family structure and perform GWAS analysis with great power, additional models are still required to provide support for the GWAS results. Family-based association test for quantitative traits (QFAM) in PLINK (Abecasis et al. 2000; Purcell et al. 2007) and family-based score test for association (FASTA) in GenABEL (Aulchenko et al. 2007; Chen and Abecasis 2007) were conducted separately to validate the identification of

QTLs from EMMAX. QFAM has been proved to provide enough statistical power for GWAS analysis in catfish family-based samples (Geng et al. 2016, 2017; Zhou et al. 2017), and FASTA could utilize both genomic kinship matrix and pedigree kinship matrix to perform GWAS analyses based on polygenic mixed model (Chen and Abecasis 2007). Manhattan plots were produced using qqman (Turner 2014) and GenABEL, respectively.

Conditional analyses were carried out to examine the correlation of the SNPs associated with body weight. The most significant SNP on each linkage group was separately included in the association analysis as a covariate. Manhattan plots were generated using SVS software package to observe the $-\log_{10}(P \text{ value})$ of the other SNPs.

Candidate genes

The genes within the significantly associated genomic region (~ 1 Mb) with body weight were identified using the catfish reference genome (Liu et al. 2016) and examined for candidate genes according to their functions. Genomicus v85.01 (Muffato et al. 2010) was used to construct the synteny of several identified genes from pig and human to provide evidence for orthology. The genes closest to the suggestive SNPs were also examined and analyzed for their functions in growth.

Results

Phenotypic variation

The final data used for the GWAS contained 192,204 QC-filtered SNPs genotyped in 556 fish from nine families with body weight measured approximately 1-year post-hatching. The nine families are described in Table 1, from which 10–106 individuals were used in this study. The Wright's F_{st} statistics between each pair of families ranged from 0.03 to 0.34 (Table S2), indicating their relatively high genetic relatedness. Body weight was measured as phenotypic data ranging from 13 to 180 g with an average of 51 g (Table 1).

Genomic regions associated with body weight

A Manhattan plot based on EMMAX method is shown in Fig. 1, identifying 22 SNPs on linkage group 5 significantly associated with body weight ($-\log_{10}(P \text{ value}) > 5.19$). These SNPs are located in a genomic region from 5,450,551 to 6,564,089 bp, spanning approximately 1.1 Mb. As shown in Table 2, their minor allele frequencies ranged from 0.06 to 0.49. The most significant SNP explained 6.72% of phenotypic variation.

Four genomic regions on linkage group 1, 2, 23 and 24 were found to be suggestively associated with body weight ($-\log_{10}(P \text{ value}) > 3.89$), but were not statistically significant at the genome level. As shown in Table 3, linkage group 1 harbored quite a few SNPs in a long-range genomic region from 1,777,673 to 3,935,580 bp, with $-\log_{10}(P \text{ value})$ ranging from 3.90 to 4.51. Similarly, linkage group 23 and

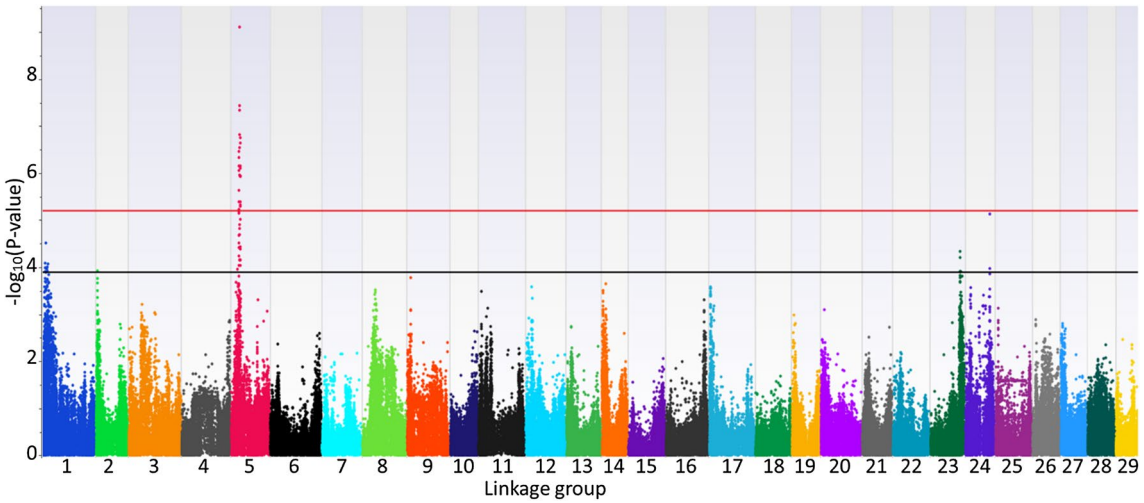

Fig. 1 Manhattan plot of genome-wide association analysis for body weight by EMMAX in SVS. The red solid line indicates the genome-wide significant threshold: $-\log_{10}(P \text{ value}) = 5.19$. The black solid line indicates the threshold for the significance of "suggestive association": $-\log_{10}(P \text{ value}) = 3.89$. (Color figure online)

Table 2 The significantly associated SNPs for growth

SNP ID	Linkage group	Position (bp)	MAF[b]	*P* value	$-\log_{10}(P \text{ value})$	PVE[c] (%)
AX-85292442	LG[a]5	5,450,551	0.07	4.21E−06	5.38	3.82
AX-86103013	LG[a]5	5,513,789	0.49	6.18E−06	5.21	3.69
AX-85395390	LG[a]5	5,538,164	0.10	2.37E−06	5.63	4.01
AX-85355896	LG[a]5	5,559,855	0.32	7.21E−07	6.14	4.42
AX-85407973	LG[a]5	5,563,633	0.20	9.15E−07	6.04	4.34
AX-85345660	LG[a]5	5,664,085	0.06	3.49E−07	6.46	4.66
AX-85302783	LG[a]5	5,702,991	0.10	4.82E−07	6.32	4.55
AX-85226693	LG[a]5	5,734,708	0.31	1.55E−07	6.81	4.94
AX-85934069	LG[a]5	5,734,825	0.22	7.85E−10	9.11	6.72
AX-85265654	LG[a]5	5,757,941	0.18	3.82E−08	7.42	5.41
AX-85190477	LG[a]5	5,910,432	0.18	4.75E−08	7.32	5.34
AX-85411013	LG[a]5	6,086,388	0.10	1.14E−06	5.94	4.26
AX-85243796	LG[a]5	6,185,149	0.20	2.90E−07	6.54	4.73
AX-85412389	LG[a]5	6,409,325	0.49	2.32E−07	6.63	4.80
AX-85240146	LG[a]5	6,414,367	0.41	1.81E−07	6.74	4.89
AX-85335866	LG[a]5	6,417,114	0.46	7.93E−07	6.10	4.39
AX-85263876	LG[a]5	6,461,776	0.08	1.22E−06	5.91	4.24
AX-85301761	LG[a]5	6,484,466	0.08	7.17E−07	6.14	4.42
AX-85404447	LG[a]5	6,498,364	0.42	4.15E−06	5.38	3.82
AX-85315779	LG[a]5	6,516,984	0.07	5.30E−06	5.28	3.74
AX-86020715	LG[a]5	6,543,107	0.28	4.87E−06	5.31	3.77
AX-85945508	LG[a]5	6,564,089	0.08	1.16E−06	5.93	4.25

[a]*LG* linkage group

[b]*MAF* minor allele frequency

[c]*PVE* phenotypic variation explained

Table 3 The suggestively associated SNPs for growth

SNP ID	Linkage group	Position (bp)	MAF[b]	*P* value	$-\log_{10}(P \text{ value})$	PVE[c] (%)
AX-85224792	LG[a]1	1,777,673	0.25	1.25E−04	3.90	2.67
AX-85291341	LG[a]1	1,901,215	0.42	1.04E−04	3.98	2.73
AX-85267456	LG[a]1	1,923,556	0.25	8.33E−05	4.08	2.81
AX-85399862	LG[a]1	2,211,229	0.22	3.09E−05	4.51	3.14
AX-85352659	LG[a]1	2,724,541	0.42	1.07E−04	3.97	2.72
AX-85444694	LG[a]1	2,988,826	0.42	1.07E−04	3.97	2.72
AX-85405675	LG[a]1	3,334,074	0.39	1.21E−04	3.92	2.67
AX-85338398	LG[a]1	3,440,382	0.38	1.01E−04	4.00	2.74
AX-85219473	LG[a]1	3,935,580	2.57	8.58E−05	4.07	2.80
AX-86013626	LG[a]2	961,642	0.25	1.22E−04	3.91	2.68
AX-85213196	LG[a]23	21,265,035	0.45	4.66E−05	4.33	3.01
AX-85352267	LG[a]23	21,311,535	0.44	6.46E−05	4.19	2.89
AX-86101139	LG[a]23	21,312,292	0.44	1.25E−04	3.90	2.67
AX-85201015	LG[a]23	21,644,603	0.43	1.27E−04	3.90	2.67
AX-85954590	LG[a]24	17,073,975	0.25	7.51E−06	5.12	3.62
AX-85383871	LG[a]24	17,357,183	0.35	1.07E−04	3.97	2.70

[a]*LG* linkage group

[b]*MAF* minor allele frequency

[c]*PV*E phenotypic variation explained

24 contained several SNPs reaching suggestive genome wide significance, spanning short ranges from 21,265,035 to 21,644,603 bp and from 17,073,975 to 17,357,183 bp, respectively. There is one SNP at position 961,642 bp on the linkage group 2 suggestively associated with growth.

Manhattan plots based on QFAM and FASTA methods (genomic kinship matrix) are shown in Fig. 2, identifying the same genomic region significantly associated with body weight on linkage group 5. This further confirmed the accuracy of EMMAX and the significance of this region on linkage group 5 in catfish growth. Genomic regions on linkage group 1, 23 and 24 were also found to be suggestively associated with body weight by both methods (Fig. 2). Differently, QFAM identified a wider region on linkage group 1, while FASTA identified more regions on linkage groups 3, 14, 16, 17 and 22 reaching suggestive association threshold. Compared with the results based on genomic kinship matrix, FASTA using pedigree kinship matrix could not effectively detect the QTL significantly associated with body weight (Figure S1). Genomic kinship matrix seems to provide better estimate of a covariance between individuals and thus has more power to detect QTL in GWAS analysis.

Correlation of the SNPs associated with growth

Conditional analyses were conducted to evaluate the correlation of the SNPs associated with body weight (Geng et al. 2015). The $-\log_{10}(P \text{ value})$ of the associated SNPs dropped below 2.5 after the most significant SNP (AX-85934069) on linkage group 5 was included as a covariate while the other SNPs remained unchanged on the other linkage groups (not shown), which indicated the strong correlations of the associated SNPs with body weight. Similarly, there were also strong correlations among those associated SNPs on the other linkage groups. These correlations suggested that the associated SNPs in the same genomic region are most likely associated with a single QTL; they were significant simply because of their linkage. Therefore, the most significant SNP was selected to represent the genomic region to obtain the ratio of

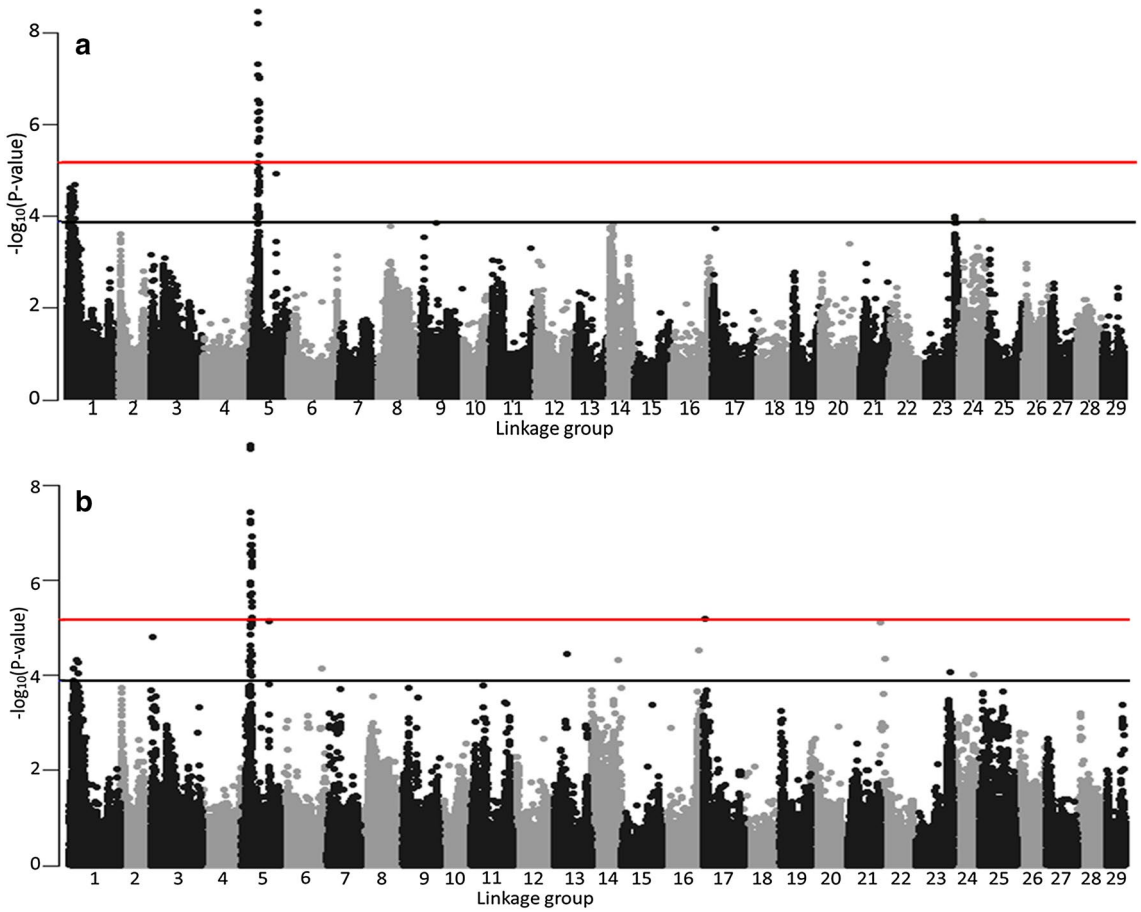

Fig. 2 Manhattan plot of genome-wide association analysis for body weight by **a** QFAM in PLINK and **b** FASTA based on genomic kinship matrix in GenABEL. The red solid line indicates the genome-wide significant threshold: $-\log_{10}(P \text{ value}) = 5.19$. The black solid line indicates the threshold for the significance of "suggestive association": $-\log_{10}(P \text{ value}) = 3.89$. (Color figure online)

phenotypic variation explained by the QTL. The phenotypic variation explained by the most significant SNP on linkage group 5 is 6.72%. Additionally, four suggestive QTL on linkage group 1, 2, 23 and 24 could explain 3.14, 2.68, 3.01 and 3.62%, respectively. Collectively, these significant and suggestively significant QTL can account for 19.17% phenotypic variation.

Genes within the significant QTL region for growth

Since the reference genome sequence is available, we determined the genes within the region containing significant SNPs (Fig. 3). Twenty-one genes including duplications of two genes are present in the genomic region harboring the significant SNPs on linkage group 5 associated with body weight (Fig. 3, Table S3). Of the non-redundant 19 genes, six were found to have known functions in growth or associated with growth-related traits in humans and pigs, including ryanodine receptor 2 (*ryr2*), alpha actinin 2 (*actn2*), glutathione peroxidase 6 (*gpx6*), disintegrin and metalloproteinase domain 12 (*adam12*), dedicator of cytokinesis 1 (*dock1*) and family with sequence similarity 196 member A (*fam196a*).

Discussion

In this work, we used GWAS and identified one significant QTL and four additional suggestive QTL for catfish growth. Because the reference genome sequence was available, it was possible for us to determine the genes included in the QTL regions. This is the first GWA study in catfish that identified growth-related QTLs and some novel candidate genes which have never been found to affect growth in fish species. These findings may provide genetic basis for better understanding the molecular mechanisms in regulation of growth in teleosts.

We were surprised to have identified only one significant QTL associated with body weight and this finding was further confirmed by another two different methods (QFAM and FASTA), which indicated the significance of this QTL in catfish growth. Because the interspecific hybrid backcross progenies were used for the GWAS analysis, the identified genetic signal could be due to differences in channel catfish and blue catfish genomes (i.e., different alleles in each species). Since multiple strains of channel catfish have been applied to study QTL associated with hypoxia using the same 250 K SNP array (Wang et al. 2016a), those significant markers were examined in the channel catfish populations. The searching results suggested that the significant SNPs were polymorphic in all the channel catfish strains,

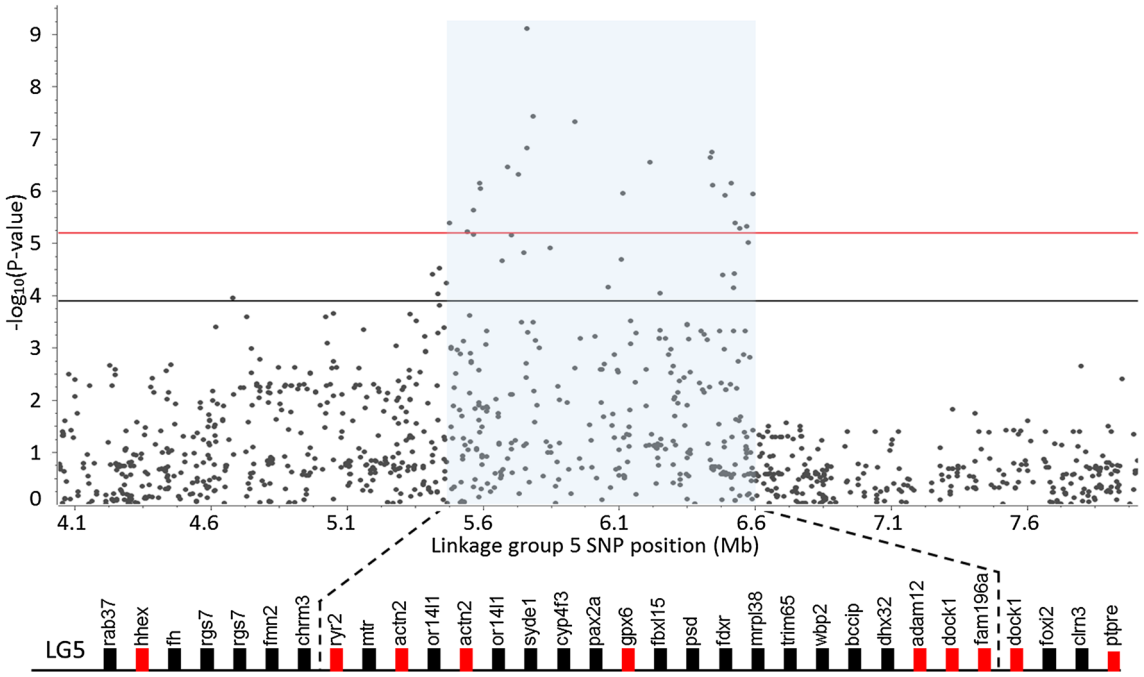

Fig. 3 Regional genome scan for the QTL significantly associated with body weight on linkage group 5. The blue shade indicates the associated genomic region. The horizontal red line indicates the threshold for genome-wide significance ($-\log_{10}(P$ value$)=5.19$). The horizontal black line indicates the threshold for the significance of "suggestive association" ($-\log_{10}(P$ value$)=3.89$). The boxes of candidate genes are marked in red. (Color figure online)

suggesting that the growth QTL is not functioning at the species level, but variable within channel catfish and blue catfish.

The most significant SNP on linkage group 5 was estimated to account for 6.72% of phenotypic variation. The small percentage may suggest that growth is under the control of a number of genes. The use of multiple families could have increased the environmental variations that affected the growth trait. To provide a better estimation of the ratio of its accounted phenotypic variation, use of larger populations is required. The sample size of the present study was limited by financial restrictions because of the costs of the SNP arrays. Similarly, those percentages of phenotypic variation estimated for the suggestive QTL likely were also underestimated.

The use of well-structured families for QTL analysis likely increased the chances of detecting QTL because phenotypic variations were under control. The use of a large number of families should have also increased the odds of narrowing the QTL to smaller genomic regions. However, the use of family-based individuals, instead of random and unrelated fish, prohibited fine mapping of the QTL because of long haplotype blocks in the backcross progenies (Geng et al. 2016). Although the high-density SNP array was effective for the GWAS analysis, the resolution was mainly limited by the number of individuals used in this study, and by the lack of recombination within the QTL region.

Once the QTL is mapped to a small physical region in the genome, genes in such associated regions can be readily determined with the catfish reference genome sequence (Liu et al. 2016). Nineteen non-redundant genes were present within the genomic region containing significant SNPs on linkage group 5 (Fig. 3). Due to the lack of high resolution of the mapping powers, we do not know which of these genes, and even some other genes at a nearby genomic location outside of this region, are likely to be the causal gene. However, a close examination of the gene identities and their known functions provided some insights into the potential candidate genes. For instance, eight genes in the associated region and extended regions on linkage group 5 were known to have functions in growth or associated with growth-related traits in other organisms. *Hhex* is a critical regulator of development and in zebrafish it is required for hemangioblast differentiation, liver specification and especially the formation of body axis (Ho et al. 1999; Liao et al. 2000; Bischof and Driever 2004; Shin et al. 2007; Soufi and Jayaraman 2008), during which it may affect early growth-related traits. *Ryr2* regulates calcium release from sarcoplasmic reticulum in cardiomyocytes, playing an integral role in cardiac myocyte contraction (Taur and Frishman 2005). Moreover, a mouse model with *ryr2* knocked in showed accelerated development of cardiac hypertrophy (van Oort et al. 2010). Similarly, its paralog *ryr1* also has an effect on muscle hypertrophy with being associated with *ifg2* (Stinckens et al. 2007), and it is positively associated with increased percentage of lean meat in pigs (Pommier et al. 1998; Stinckens et al. 2009). Interestingly, the hypertrophy of fish muscle fibers contributes greatly to the massive increase of girth between hatching and maturity (Johnston 1999). There is another gene, *actn2*, in the genomic region, which was known to cause muscle hypertrophy. Mutations in *actn2* were reported to be related to hypertrophic cardiomyopathy and dilated cardiomyopathy with hypertrophic myocardium in human (Mohapatra et al. 2003; Chiu et al. 2010). In addition, *actn2* is a major structural component of sarcomeric Z-lines where it functions to organize actin filaments in a constitutive manner (Beggs et al. 1992). In vitro studies in cell culture demonstrated that deletion mutants of *actn2* led to disruption of myofibrils, indicating its role in skeletal muscle assembly and maintenance (Schultheiss et al. 1992). In addition, *actn2* could interact with different classes of cytoskeletal and regulatory proteins to maintain the structure and functions of skeletal muscle (Faulkner et al. 2001; Clark et al. 2002; Sjöblom et al. 2008). *Adam12* is another gene affecting muscle development and functions. Overexpression of *adam12* in the mice with muscular dystrophy could alleviate the skeletal muscle pathology, contributing to muscle regeneration (Kronqvist et al. 2002). Interestingly, Galliano et al. (Galliano et al. 2000) found that binding of *adam12* to *actn2* is required for myoblast fusion which is a key process for formation and repair of muscle. Moreover, *adam12* was also found to be expressed in human and mouse bone cells including osteoblasts and osteoclasts (Inoue et al. 1998; Abe et al. 1999; Boissy et al. 2003; Verrier et al. 2004), suggesting its regulatory role in bone development. One pronounced example is that a*dam12* transgenic mice exhibited an increase in the longitudinal bone length including femur, tibia and vertebrae through regulating chondrocyte proliferation and maturation (Kveiborg et al. 2006). Furthermore, *adam12*-knockout zebrafish exhibited reduced body size during juvenile stage without defects in morphology, indicating the possible role of *adam12* in affecting cartilage/bone development (Tokumasu et al. 2016). In addition to *adam12, dock1* is another gene modulating myoblast fusion, which was well characterized in its homologue myoblast city (*mbc*) gene in *Drosophila* (Erickson et al. 1997). Both *dock1*-knockdown zebrafish embryo and *dock1*-null mouse embryo exhibited reduction in skeletal muscle, which is attributed to defective myoblast fusion (Moore et al. 2007; Laurin et al. 2008). Its paralog, *dock5*, is also a critical regulator during myoblast fusion process (Moore et al. 2007; Laurin et al. 2008). PBX homeobox 4 (*pbx4*) was identified close to the most significant SNP in the suggestively associated region on linkage group 24. The homeodomain proteins *pbx* are important in modulating skeletal myogenesis, inhibitions of which in zebrafish embryos affected the

development of fast muscle (Maves et al. 2007; Yao et al. 2013). Although it is unknown which of these genes is the causal gene, the involvement of these genes within the QTL in muscle growth and bone development provided additional support of the QTL as truly affecting growth.

There appears to be evolutionary conservation of the genes involved in growth. Several genes within the QTL region were known to be associated with growth in other organisms. *Gpx6* was found to be positively associated with obesity in Spanish children (Rupérez et al. 2014), and its paralogs (*gpx1, gpx4* and *gpx5*) were also observed in close relationship with obesity in animal and human studies (Asayama et al. 2001; Ozgen et al. 2012; Rupérez et al. 2014). Alaska native population was also analyzed for obesity traits, suggesting that *dock1* and *ptpre* were potential candidate genes (Vaughan et al. 2015). Interestingly, their paralogs (*dock5, ptpra, ptprd* and *ptprf*) have been long known as obesity susceptibility genes (Ahmad et al. 1997; Moustafa et al. 2012). Another association study was carried out for pig birth weight, showing that *ptpre* and *fam196a* were close to the significantly associated SNP (Wang et al. 2016b). Syntenic conservation among catfish, human and pig (Fig. 4) with *adam12, dock1, fam196a* and *ptpre* all in the conserved syntenic block indicated that the functions of these genes may be evolutionarily conserved.

In addition to the evolutionary conservation of the genes discussed above involved in growth among catfish and mammals, several genes associated with growth in catfish identified in this study were also reported to be associated with QTL for growth in several teleost species. GWAS or QTL mapping analysis for growth was reported in Atlantic salmon (Gutierrez et al. 2015; Tsai et al. 2015), orange-spotted grouper (Yu et al. 2016), Arctic charr (Moghadam et al. 2007), rainbow trout (Wringe et al. 2010), Asian seabass (Wang et al. 2008, 2011, 2015; Xia et al. 2013), European seabass (Louro et al. 2016), common carp (Lv et al. 2016; Peng et al. 2016), bighead carp (Fu et al. 2016), turbot (Sánchez-Molano et al. 2011), tilapia (Liu et al. 2014a) and catfish (Hutson et al. 2014). For the study in catfish (Hutson et al. 2014), an old linkage map was utilized and candidate gene analysis was not conducted due to absence of genome sequence, so it did not provide much useful information for comparison with our study. In those cases except catfish, there were only a handful of shared genes such as growth hormone (*GH*), growth hormone receptor (*GHR*), insulin-like growth factor (*IGF*) and myostatin (*MSTN*), all of which have been well known to be correlated with growth in finfish (DeSantis and Jerry 2007). However, several homologs of the genes identified within the QTL for growth in catfish in this study were also identified in some linkage mapping studies for growth, such as *pax7* from rainbow trout (Wringe et al. 2010), *foxk2* from common carp (Lv et al. 2016), *rgs7, trim16* and *trim41* from Tilapia (Liu et al. 2014a). Once again, these results suggested evolutionary conservation of genes and their functions across species.

In summary, we identified a single significant QTL on linkage group 5 for growth traits, and four suggestive QTL on linkage groups 1, 2, 23, and 24. The causal gene for growth is unknown at the present, but the nine genes known to have functions in growth or associated with growth traits within the mapped QTL region are potential candidates. Future studies are required to fine map the QTL, toward the identification of the causal gene. Nonetheless, there appeared to be evolutionary conservation of the genes controlling growth among fish and various mammals. In addition to fine mapping, comparative quantitative genomics may lend some additional powers for the identification of the causal gene for growth traits.

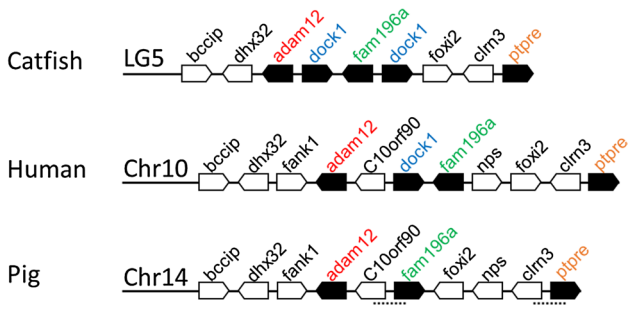

Fig. 4 Conserved synteny blocks of some candidate genes associated with body weight in catfish, human and pig. Homologs in different species are marked with the same color. Solid black boxes indicate the candidate genes. The two directions of genes indicate the different DNA strands they are located on. Dash lines under the boxes in the pig synteny block indicate some genes are not shown due to the absence of homologs in the other two species

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures involving the handling and treatment of fish were approved by the Institutional Animal Care and Use Committee (IACUC) at Auburn University.

References

Abe E, Mocharla H, Yamate T, Taguchi Y, Manolagas S (1999) Meltrin-α, a fusion protein involved in multinucleated giant cell and osteoclast formation. Calcif Tissue Int 64:508–515

Abecasis GR, Cardon LR, Cookson W (2000) A general test of association for quantitative traits in nuclear families. Am J Hum Genet 66:279–292

Ahmad F, Azevedo J, Cortright R, Dohm GL, Goldstein BJ (1997) Alterations in skeletal muscle protein-tyrosine phosphatase activity and expression in insulin-resistant human obesity and diabetes. J Clin Investig 100:449

Asayama K, Nakane T, Dobashi K, Kodera K, Hayashibe H, Uchida N, Nakazawa S (2001) Effect of obesity and troglitazone on expression of two glutathione peroxidases: cellular and extracellular types in serum, kidney and adipose tissue. Free Radic Res 34:337–347

Aulchenko YS, Ripke S, Isaacs A, Van Duijn CM (2007) GenABEL: an R library for genome-wide association analysis. Bioinformatics 23:1294–1296

Beggs AH, Byers TJ, Knoll J, Boyce FM, Bruns G, Kunkel LM (1992) Cloning and characterization of two human skeletal muscle alpha-actinin genes located on chromosomes 1 and 11. J Biol Chem 267:9281–9288

Bischof J, Driever W (2004) Regulation of hhex expression in the yolk syncytial layer, the potential Nieuwkoop center homolog in zebrafish. Dev Biol 276:552–562

Boissy P, Lenhard TR, Kirkegaard T, Peschon JJ, Black RA, Delaissé J-M, del Carmen Ovejero M (2003) An assessment of ADAMs in bone cells: absence of TACE activity prevents osteoclast recruitment and the formation of the marrow cavity in developing long bones. FEBS Lett 553:257–261

Chen W-M, Abecasis GR (2007) Family-based association tests for genomewide association scans. Am J Hum Genet 81:913–926

Chiu C, Bagnall RD, Ingles J, Yeates L, Kennerson M, Donald JA, Jormakka M, Lind JM, Semsarian C (2010) Mutations in alpha-actinin-2 cause hypertrophic cardiomyopathy: a genome-wide analysis. J Am Coll Cardiol 55:1127–1135

Clark KA, McElhinny AS, Beckerle MC, Gregorio CC (2002) Striated muscle cytoarchitecture: an intricate web of form and function. Annu Rev Cell Dev Biol 18:637–706

Clay LA, Wang SY, Wolters WR, Peterson BC, Waldbieser GC (2005) Molecular characterization of the insulin-like growth factor-I (IGF-I) gene in channel catfish (*Ictalurus punctatus*). BBA Gene Struct Express 1731:139–148

De-Santis C, Jerry DR (2007) Candidate growth genes in finfish—where should we be looking? Aquaculture 272:22–38

Du SJ, Gong Z, Fletcher GL, Shears MA, King MJ, Idler DR, Hew CL (1992) Growth enhancement in transgenic Atlantic salmon by the use of an "all fish" chimeric growth hormone gene construct. Nat Biotechnol 10:176–181

Duggal P, Gillanders EM, Holmes TN, Bailey-Wilson JE (2008) Establishing an adjusted p-value threshold to control the family-wide type 1 error in genome wide association studies. BMC Genom 9:1

Dunham RA, Masser MP (2012) Production of hybrid catfish. Southern Regional Aquaculture Center. Stoneville, MS

Dunham R, Ramboux A, Duncan P, Hayat M, Chen T, Lin C, Kight K, Gonzalez-Villasenor I, Powers D (1991) Transfer, expression, and inheritance of salmonid growth hormone genes in channel catfish, *Ictalurus punctatus*, and effects on performance traits. Mol Mar Biol Biotechnol 1:380–389

Erickson MRS, Galletta BJ, Abmayr SM (1997) Drosophila myoblast city encodes a conserved protein that is essential for myoblast fusion, dorsal closure, and cytoskeletal organization. J Cell Biol 138:589–603

FAO (2016) FAO yearbook. Fishery and Aquaculture Statistics 2014

Faulkner G, Lanfranchi G, Valle G (2001) Telethonin and other new proteins of the Z-disc of skeletal muscle. IUBMB Life 51:275–282

Feng X, Yu X, Pang M, Liu H, Tong J (2015) Molecular characterization and expression of three preprosomatostatin genes and their association with growth in common carp (*Cyprinus carpio*). Comp Biochem Physiol Part B Biochem Mol Biol 182:37–46

Fu B, Liu H, Yu X, Tong J (2016) A high-density genetic map and growth related QTL mapping in bighead carp (*Hypophthalmichthys nobilis*). Sci Rep 6:28679

Galliano M-F, Huet C, Frygelius J, Polgren A, Wewer UM, Engvall E (2000) Binding of ADAM12, a marker of skeletal muscle regeneration, to the muscle-specific actin-binding protein, α-actinin-2, is required for myoblast fusion. J Biol Chem 275:13933–13939

Geng X, Sha J, Liu S, Bao L, Zhang J, Wang R, Yao J, Li C, Feng J, Sun F (2015) A genome-wide association study in catfish reveals the presence of functional hubs of related genes within QTLs for columnaris disease resistance. BMC Genom 16:1

Geng X, Liu S, Yao J, Bao L, Zhang J, Li C, Wang R, Sha J, Zeng P, Zhi D (2016) A genome wide association study identifies multiple regions associated with head size in catfish. G36:3389–3398

Geng X, Liu S, Yuan Z, Jiang Y, Zhi D, Liu Z (2017) A genome-wide association study reveals that genes with functions for bone development are associated with body conformation in catfish. Mar Biotechnol 19:570–578

Gutierrez AP, Yanez JM, Fukui S, Swift B, Davidson WS (2015) Genome-wide association study (GWAS) for growth rate and age at sexual maturation in Atlantic salmon (*Salmo salar*). PLoS One 10:e0119730

Ho C-Y, Houart C, Wilson SW, Stainier DY (1999) A role for the extraembryonic yolk syncytial layer in patterning the zebrafish embryo suggested by properties of the hex gene. Curr Biol 9:1131-S1134

Hu X, Li C, Shi L (2013) A novel 79-bp insertion/deletion polymorphism in 3′-flanking region of IGF-I gene is associated with growth-related traits in common carp (*Cyprinus carpio* L.). Aquac Res 44:1632–1638

Hutson A, Liu Z, Kucuktas H, Umali-Maceina G, Su B, Dunham R (2014) Quantitative trait loci map for growth and morphometric traits using a channel catfish × blue catfish interspecific hybrid system. J Anim Sci 92:1850–1865

Inoue D, Reid M, Lum L, Krätzschmar J, Weskamp G, Myung YM, Baron R, Blobel CP (1998) Cloning and initial characterization of mouse meltrin β and analysis of the expression of four metalloproteasedisintegrins in bone cells. J Biol Chem 273:4180–4187

Jin Y, Zhou T, Geng X, Liu S, Chen A, Yao J, Jiang C, Tan S, Su B, Liu Z (2016) A genome-wide association study of heat stress-associated SNPs in catfish. Anim Genet. 48:233–236

Johnston IA (1999) Muscle development and growth: potential implications for flesh quality in fish. Aquaculture 177:99–115

Kang JH, Lee SJ, Park SR, Ryu HY (2002) DNA polymorphism in the growth hormone gene and its association with weight in olive flounder *Paralichthys olivaceus*. Fish Sci 68:494–498

Kang HM, Sul JH, Service SK, Zaitlen NA, Kong S-y, Freimer NB, Sabatti C, Eskin E (2010) Variance component model to account for sample structure in genome-wide association studies. Nat Genet 42:348–354

Kocabas AM, Kucuktas H, Dunham RA, Liu Z (2002) Molecular characterization and differential expression of the myostatin gene in channel catfish (*Ictalurus punctatus*). BBA Gene Struct Express 1575:99–107

Kronqvist P, Kawaguchi N, Albrechtsen R, Xu X, Schrøder HD, Moghadaszadeh B, Nielsen FC, Fröhlich C, Engvall E, Wewer

UM (2002) ADAM12 alleviates the skeletal muscle pathology in mdx dystrophic mice. Am J Pathol 161:1535–1540

Kucuktas H, Wang S, Li P, He C, Xu P, Sha Z, Liu H, Jiang Y, Baoprasertkul P, Somridhivej B (2009) Construction of genetic linkage maps and comparative genome analysis of catfish using gene-associated markers. Genetics 181:1649–1660

Kveiborg M, Albrechtsen R, Rudkjær L, Wen G, Damgaard-Pedersen K, Wewer UM (2006) ADAM12-S stimulates bone growth in transgenic mice by modulating chondrocyte proliferation and maturation. J Bone Miner Res 21:1288–1296

Laghari MY, Zhang Y, Lashari P, Zhang X, Xu P, Xin B, Sun X (2013) Quantitative trait loci (QTL) associated with growth rate trait in common carp (*Cyprinus carpio*). Aquacult Int 21:1373–1379

Laghari MY, Lashari P, Zhang X, Xu P, Xin B, Zhang Y, Narejo NT, Sun X (2014) Mapping quantitative trait loci (QTL) for body weight, length and condition factor traits in backcross (BC1) family of Common carp (*Cyprinus carpio* L.). Mol Biol Rep 41:721–731

Laurin M, Fradet N, Blangy A, Hall A, Vuori K, Côté J-F (2008) The atypical Rac activator Dock180 (*Dock1*) regulates myoblast fusion in vivo. Proc Natl Acad Sci 105:15446–15451

Li Y, Liu S, Qin Z, Waldbieser G, Wang R, Sun L, Bao L, Danzmann RG, Dunham R, Liu Z (2014) Construction of a high-density, high-resolution genetic map and its integration with BAC-based physical map in channel catfish. DNA Res 22:39–52

Liao W, Ho C-Y, Yan YL, Postlethwait J, Stainier D (2000) *Hhex* and *scl* function in parallel to regulate early endothelial and blood differentiation in zebrafish. Development 127:4303–4313

Liu Z, Karsi A, Li P, Cao D, Dunham R (2003) An AFLP-based genetic linkage map of channel catfish (*Ictalurus punctatus*) constructed by using an interspecific hybrid resource family. Genetics 165:687–694

Liu F, Sun F, Xia JH, Li J, Fu GH, Lin G, Tu RJ, Wan ZY, Quek D, Yue GH (2014a) A genome scan revealed significant associations of growth traits with a major QTL and GHR2 in tilapia. Sci Rep 4:7256

Liu S, Sun L, Li Y, Sun F, Jiang Y, Zhang Y, Zhang J, Feng J, Kaltenboeck L, Kucuktas H (2014b) Development of the catfish 250K SNP array for genome-wide association studies. BMC Res Notes 7:1

Liu Z, Liu S, Yao J, Bao L, Zhang J, Li Y, Jiang C, Sun L, Wang R, Zhang Y, Zhou T, Zeng Q, Fu Q, Gao S, Li N, Koren S, Jiang Y, Zimin A, Xu P, Phillippy AM, Geng X, Song L, Sun F, Li C, Wang X, Chen A, Jin Y, Yuan Z, Yang Y, Tan S, Peatman E, Lu J, Qin Z, Dunham R, Li Z, Sonstegard T, Feng J, Danzmann RG, Schroeder S, Scheffler B, Duke MV, Ballard L, Kucuktas H, Kaltenboeck L, Liu H, Armbruster J, Xie Y, Kirby ML, Tian Y, Flanagan ME, Mu W, Waldbieser GC (2016) The channel catfish genome sequence provides insights into the evolution of scale formation in teleosts. Nat Commun 7:11757

Louro B, Kuhl H, Tine M, de Koning D-J, Batargias C, Volckaert FAM, Reinhardt R, Canario AVM, Power DM (2016) Characterization and refinement of growth related quantitative trait loci in European sea bass (*Dicentrarchus labrax*) using a comparative approach. Aquaculture 455:8–21

Lv W, Zheng X, Kuang Y, Cao D, Yan Y, Sun X (2016) QTL variations for growth-related traits in eight distinct families of common carp (*Cyprinus carpio*). BMC Genet 17:65

Maves L, Waskiewicz AJ, Paul B, Cao Y, Tyler A, Moens CB, Tapscott SJ (2007) Pbx homeodomain proteins direct Myod activity to promote fast-muscle differentiation. Development 134:3371–3382

McPherron AC, Lee S-J (1997) Double muscling in cattle due to mutations in the myostatin gene. Proc Natl Acad Sci 94:12457–12461

McRory JE, Parker DB, Ngamvongchon S, Sherwood NM (1995) Sequence and expression of cDNA for pituitary adenylate cyclase activating polypeptide (PACAP) and growth hormone-releasing hormone (GHRH)-like peptide in catfish. Mol Cell Endocrinol 108:169–177

Moghadam HK, Poissant J, Fotherby H, Haidle L, Ferguson MM, Danzmann RG (2007) Quantitative trait loci for body weight, condition factor and age at sexual maturation in Arctic charr (*Salvelinus alpinus*): comparative analysis with rainbow trout (*Oncorhynchus mykiss*) and Atlantic salmon (*Salmo salar*). Mol Genet Genom 277:647–661

Mohapatra B, Jimenez S, Lin JH, Bowles KR, Coveler KJ, Marx JG, Chrisco MA, Murphy RT, Lurie PR, Schwartz RJ (2003) Mutations in the muscle LIM protein and α-actinin-2 genes in dilated cardiomyopathy and endocardial fibroelastosis. Mol Genet Metab 80:207–215

Moore CA, Parkin CA, Bidet Y, Ingham PW (2007) A role for the Myoblast city homologues *Dock1* and *Dock5* and the adaptor proteins *Crk* and *Crk*-like in zebrafish myoblast fusion. Development 134:3145–3153

Moustafa JSE-S., Eleftherohorinou H, de Smith AJ, Andersson-Assarsson JC, Alves AC, Hadjigeorgiou E, Walters RG, Asher JE, Bottolo L, Buxton JL (2012) Novel association approach for variable number tandem repeats (VNTRs) identifies DOCK5 as a susceptibility gene for severe obesity. Hum Mol Genet 21:3727–3738

Muffato M, Louis A, Poisnel C-E, Crollius HR (2010) Genomicus: a database and a browser to study gene synteny in modern and ancestral genomes. Bioinformatics 26:1119–1121

Nei M (1973) Analysis of gene diversity in subdivided populations. Proc Natl Acad Sci 70:3321–3323

Ozgen IT, Tascilar ME, Bilir P, Boyraz M, Guncikan MN, Akay C, Dundaroz R (2012) Oxidative stress in obese children and its relation with insulin resistance. J Pediatr Endocrinol Metab 25:261–266

Peng W, Xu J, Zhang Y, Feng J, Dong C, Jiang L, Feng J, Chen B, Gong Y, Chen L, Xu P (2016) An ultra-high density linkage map and QTL mapping for sex and growth-related traits of common carp (*Cyprinus carpio*). Sci Rep 6:26693

Peterson BC, Small BC, Waldbieser GC, Bosworth BG (2008) Endocrine responses of fast-and slow-growing families of channel catfish. N Am J Aquacult 70:240–250

Pommier SA, Pomar C, Godbout D (1998) Effect of the halothane genotype and stress on animal performance, carcass composition and meat quality of crossbred pigs. Can J Anim Sci 78:257–264

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, De Bakker PI, Daly MJ (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 81:559–575

Renaville R, Hammadi M, Portetelle D (2002) Role of the somatotropic axis in the mammalian metabolism. Domest Anim Endocrinol 23:351–360

Richmond JP, Norris T, Zinn SA (2010) Re-alimentation in harbor seal pups: effects on the somatotropic axis and growth rate. Gen Comp Endocrinol 165:286–292

Robledo D, Fernandez C, Hermida M, Sciara A, Alvarez-Dios JA, Cabaleiro S, Caamano R, Martinez P, Bouza C (2016) Integrative transcriptome, genome and quantitative trait loci resources identify single nucleotide polymorphisms in candidate genes for growth traits in turbot. Int J Mol Sci 17:243

Rupérez AI, Olza J, Gil-Campos M, Leis R, Mesa MD, Tojo R, Cañete R, Gil A, Aguilera CM (2014) Association of genetic polymorphisms for glutathione peroxidase genes with obesity in spanish children. J Nutrigenet Nutrigenom 7:130–142

Sánchez-Molano E, Cerna A, Toro MA, Bouza C, Hermida M, Pardo BG, Cabaleiro S, Fernández J, Martínez P (2011) Detection of growth-related QTL in turbot (*Scophthalmus maximus*). BMC Genom 12:1

Sánchez-Ramos I, Cross I, Mácha J, Martínez-Rodríguez G, Krylov V, Rebordinos L (2012) Assessment of tools for marker-assisted selection in a marine commercial species: significant association between MSTN-1 gene polymorphism and growth traits. Sci World J 2012:1–10

Schultheiss T, Choi J, Lin Z, DiLullo C, Cohen-Gould L, Fischman D, Holtzer H (1992) A sarcomeric alpha-actinin truncated at the carboxyl end induces the breakdown of stress fibers in PtK2 cells and the formation of nemaline-like bodies and breakdown of myofibrils in myotubes. Proc Natl Acad Sci 89:9282–9286

Shin D, Shin CH, Tucker J, Ober EA, Rentzsch F, Poss KD, Hammerschmidt M, Mullins MC, Stainier DY (2007) Bmp and Fgf signaling are essential for liver specification in zebrafish. Development 134:2041–2050

Silverstein JT, Wolters WR, Shimizu M, Dickhoff WW (2000) Bovine growth hormone treatment of channel catfish: strain and temperature effects on growth, plasma IGF-I levels, feed intake and efficiency and body composition. Aquaculture 190:77–88

Sjöblom B, Salmazo A, Djinović-Carugo K (2008) α-Actinin structure and regulation. Cell Mol Life Sci 65:2688–2701

Small BC, Nonneman D (2001) Sequence and expression of a cDNA encoding both pituitary adenylate cyclase activating polypeptide and growth hormone-releasing hormone-like peptide in channel catfish (*Ictalurus punctatus*). Gen Comp Endocrinol 122:354–363

Small BC, Peterson BC (2005) Establishment of a time-resolved fluoroimmunoassay for measuring plasma insulin-like growth factor I (IGF-I) in fish: effect of fasting on plasma concentrations and tissue mRNA expression of IGF-I and growth hormone (GH) in channel catfish (*Ictalurus punctatus*). Domest Anim Endocrinol 28:202–215

Soufi A, Jayaraman P-S (2008) PRH/Hex: an oligomeric transcription factor and multifunctional regulator of cell fate. Biochem J 412:399–413

Sternberg H, Moav B (1999) Regulation of the growth hormone gene by fish thyroid/retinoid receptors. Fish Physiol Biochem 20:331–339

Stinckens A, Van den Maagdenberg K, Luyten T, Georges M, De Smet S, Buys N (2007) The RYR1 g. 1843C>T mutation is associated with the effect of the IGF2 intron3-g.3072G>A mutation on muscle hypertrophy. Anim Genet 38:67–71

Stinckens A, Luyten T, Van den Maagdenberg K, Janssens S, De Smet S, Georges M, Buys N (2009) Interactions between genes involved in growth and muscularity in pigs: IGF-2, myostatin, ryanodine receptor 1, and melanocortin-4 receptor. Domest Anim Endocrinol 37:227–235

Sun Y, Li Q, Wang G, Zhu D, Chen J, Li P, Tong J (2016) Polymorphisms in the Myostatin-1 gene and their association with growth traits in *Anchorythroculter nigrocauda*. Chin J Oceanol Limnol 35:597–602

Tan X, Du S (2002) Differential expression of two MyoD genes in fast and slow muscles of gilthead seabream (*Sparus aurata*). Dev Genes Evol 212:207–217

Tan X, Zhang Y, Zhang P-J, Xu P, Xu Y (2006) Molecular structure and expression patterns of flounder (*Paralichthys olivaceus*) *Myf-5*, a myogenic regulatory factor. Comp Biochem Physiol B Biochem Mol Biol 145:204–213

Tao W, Boulding E (2003) Associations between single nucleotide polymorphisms in candidate genes and growth rate in Arctic charr (*Salvelinus alpinus* L.). Heredity 91:60–69

Taur Y, Frishman WH (2005) The cardiac ryanodine receptor (RyR2) and its role in heart disease. Cardiol Rev 13:142–146

Tokumasu Y, Iida A, Wang Z, Ansai S, Kinoshita M, Sehara-Fujisawa A (2016) ADAM12-deficient zebrafish exhibit retardation in body growth at the juvenile stage without developmental defects. Dev Growth Diff 58:409–421

Tsai H, Hamilton A, Guy D, Houston R (2014) Single nucleotide polymorphisms in the insulin-like growth factor 1 (IGF1) gene are associated with growth-related traits in farmed Atlantic salmon. Anim Genet 45:709–715

Tsai HY, Hamilton A, Tinch AE, Guy DR, Gharbi K, Stear MJ, Matika O, Bishop SC, Houston RD (2015) Genome wide association and genomic prediction for growth traits in juvenile farmed Atlantic salmon using a high density SNP array. BMC Genom 16:969

Turner SD (2014) qqman: an R package for visualizing GWAS results using QQ and manhattan plots. BioRxiv:005165

van Oort RJ, Respress JL, Li N, Reynolds C, De Almeida AC, Skapura DG, De Windt LJ, Wehrens XH (2010) Accelerated development of pressure overload-induced cardiac hypertrophy and dysfunction in an RyR2-R176Q knockin mouse model. Hypertension 55:932–938

Vaughan LK, Wiener HW, Aslibekyan S, Allison DB, Havel PJ, Stanhope KL, O'Brien DM, Hopkins SE, Lemas DJ, Boyer BB (2015) Linkage and association analysis of obesity traits reveals novel loci and interactions with dietary n-3 fatty acids in an Alaska Native (Yup'ik) population. Metabolism 64:689–697

Verrier S, Hogan A, McKie N, Horton M (2004) ADAM gene expression and regulation during human osteoclast formation. Bone 35:34–46

Wang CM, Lo LC, Feng F, Zhu ZY, Yue GH (2008) Identification and verification of QTL associated with growth traits in two genetic backgrounds of Barramundi (*Lates calcarifer*). Anim Genet 39:34–39

Wang CM, Bai ZY, He XP, Lin G, Xia JH, Sun F, Lo LC, Feng F, Zhu ZY, Yue GH (2011) A high-resolution linkage map for comparative genome analysis and QTL fine mapping in Asian seabass, *Lates calcarifer*. BMC Genom 12:1

Wang L, Wan ZY, Bai B, Huang SQ, Chua E, Lee M, Pang HY, Wen YF, Liu P, Liu F, Sun F, Lin G, Ye BQ, Yue GH (2015) Construction of a high-density linkage map and fine mapping of QTL for growth in Asian seabass. Sci Rep 5:16358

Wang X, Liu S, Jiang C, Geng X, Zhou T, Li N, Bao L, Li Y, Yao J, Yang Y, Zhong X, Jin Y, Dunham R, Liu Z (2016a) Multiple across-strain and within-strain QTLs suggest highly complex genetic architecture for hypoxia tolerance in channel catfish. Mol Genet Genom 292:63–76

Wang X, Liu X, Deng D, Yu M, Li X (2016b) Genetic determinants of pig birth weight variability. BMC Genet 17:41

Wargelius A, Fjelldal P-G, Benedet S, Hansen T, Björnsson BT, Nordgarden U (2005) A peak in gh-receptor expression is associated with growth activation in Atlantic salmon vertebrae, while upregulation of igf-I receptor expression is related to increased bone density. Gen Comp Endocrinol 142:163–168

Weintraub H (1993) The MyoD family and myogenesis: redundancy, networks, and thresholds. Cell 75:1241–1244

Wong AO, Zhou H, Jiang Y, Ko WK (2006) Feedback regulation of growth hormone synthesis and secretion in fish and the emerging concept of intrapituitary feedback loop. Comp Biochem Physiol A Mol Integr Physiol 144:284–305

Wright S (1949) The genetical structure of populations. Ann Eugen 15:323–354

Wringe BF, Devlin RH, Ferguson MM, Moghadam HK, Sakhrani D, Danzmann RG (2010) Growth-related quantitative trait loci in domestic and wild rainbow trout (*Oncorhynchus mykiss*). BMC Genet 11:63

Xia JH, Lin G, He X, Liu P, Liu F, Sun F, Tu R, Yue GH (2013) Whole genome scanning and association mapping identified a significant association between growth and a SNP in the IFABP-a gene of the Asian seabass. BMC Genom 14:1

Yao Z, Farr GH, Tapscott SJ, Maves L (2013) Pbx and Prdm1a transcription factors differentially regulate subsets of the fast skeletal muscle program in zebrafish. Biol Open 2:546–555

Ye H, Liu Y, Liu X, Wang X, Wang Z (2014) Genetic mapping and QTL analysis of growth traits in the large yellow croaker *Larimichthys crocea*. Mar Biotechnol (NY) 16:729–738

Yu H, You X, Li J, Liu H, Meng Z, Xiao L, Zhang H, Lin HR, Zhang Y, Shi Q (2016) Genome-wide mapping of growth-related quantitative trait loci in orange-spotted grouper (*Epinephelus coioides*) using double digest restriction-site associated dna sequencing (ddRADseq). Int J Mol Sci 17:501

Zhong X, Wang X, Zhou T, Jin Y, Tan S, Jiang C, Geng X, Li N, Shi H, Zeng Q (2017) Genome-wide association study reveals multiple novel QTL associated with low oxygen tolerance in hybrid catfish. Mar Biotechnol 19:379–390

Zhou T, Liu S, Geng X, Jin Y, Jiang C, Bao L, Yao J, Zhang Y, Zhang J, Sun L (2017) GWAS analysis of QTL for enteric septicemia of catfish and their involved genes suggest evolutionary conservation of a molecular mechanism of disease resistance. Mol Genet Genom 292:231–242