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Selection for growth is associated in gilthead sea bream (*Sparus aurata*) with diet flexibility, changes in growth patterns and higher intestine plasticity

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ABSTRACT

Farmed gilthead sea bream (*Sparus aurata*) is able to grow efficiently with new feed formulations based on plant ingredients. Here, two experimental diets with standard and high inclusion levels of plant ingredients were formulated to assess the suited use of plant-based diets in fish with different growth genetic backgrounds. To pursue this issue, a long-term feeding trial (12-months) was conducted with fish (17 g initial body weight) of 16 families coming from the broodstock of PROGENSA project, that were grown communally in the IATS-CSIC experimental facilities. All fish in the study (2545) were PIT-tagged, and their pedigree was re-constructed with 96% success by using a SMsa1 multiplex of 11 microsatellites, which revealed the main parents contributions of 5 females and 6 males. Each diet was randomly assigned to replicate 3000 L tanks, gathering each replicate a similar family composition through all the feeding trial. Data on growth performance highlighted a strong genetic effect on growth trajectories, associated with enhanced growth during winter in fish selected for faster growth. No main dietary effects were found on growth rates or condition factor, and regression-correlation analyses of growth rates across families on both diets suggest that genome by diet interaction was weak, while genetic variation accounted for most of the growth phenotypic variation. Hepatosomatic index (HSI) and mesenteric fat index (MSI) of five families, covering the growth variability of the population, were regulated nutritionally and genetically, but without statistically significant genome by diet interactions. Fish from faster growing families showed shorter intestines after being fed the control diet, but this phenotype was masked by the enriched plant-based diet. Collectively, the results demonstrate that selection for faster growth is associated in gilthead sea bream with different growth trajectories and a high diet flexibility and intestine plasticity.

1. Introduction

The reliance of European aquaculture on marine feed ingredients continues to be high, though the inclusion level of marine ingredients in Norwegian salmon feeds is currently below 30% (Ytrestøyl et al., 2015). This trend is going to go further in both salmonid and non-salmonid fish, in order to assure a more sustainable aquaculture industry. For instance, rainbow trout can be grown with totally plant-based diets from first feeding onwards, with slight effects in growth performance and metabolism (Lazzarotto et al., 2018). Likewise, complete replacement of fish meal (FM) and fish oil (FO) is feasible by means of microalgae supplementation in Nile tilapia juvenile (Sarker et al., 2016). A high level of FM and FO replacement by plant ingredients has also been accomplished in typically marine fish such as the European sea bass

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(Kousoulaki et al., 2015; Torrecillas et al., 2017). Similarly, plant-based diets with < 10% marine ingredients support maximum growth from early life until completion of sexual maturation in gilthead sea bream (Benedito-Palos et al., 2016; Simó-Mirabet et al., 2018a). A high nutritional plasticity has also been reported by other authors in this protandrous hermaphroditic fish (Menoyo et al., 2004; Monge-Ortiz et al., 2016). However, changes in circulating levels of sex steroids revealed a pseudo-feminization effect of plant-based diets, with an enhanced male-female sex reversal in the presence of less powerful functional females (Simó-Mirabet et al., 2018a). In addition, both in salmon and gilthead sea bream, current plant-based diets do not represent a food safety issue for human consumers (reviewed by Nácher-Mestre et al., 2018). Moreover, low FM/FO diets do not have a major impact in fillet texture, shelf life or sensory freshness of common carp, trout and gilthead sea bream (Grigorakis et al., 2018; Turchini et al., 2018). Nevertheless, the nutritional value of fish meat is compromised in salmonid and non-salmonid fish by the use of dietary oils devoid of EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) (Menoyo et al., 2004; Turchini et al., 2009; Benedito-Palos et al., 2010; Ballester-Lozano et al., 2014). Thus, several attempts have been made for bioengineering novel EPA- and/or DHA-rich oils as alternatives to FO, with main focus on genetically engineered microalgae and oilseed crops (reviewed by Sprague et al., 2017).

Wide-serum metabolomics profiling of gilthead sea bream fed plant-based diets also highlighted changes in mucosal tissue repair and DNA degradation processes (Gil-Solsona et al., 2019). Indeed, changes on the intestinal profile of mucins, mucosal immunoglobulins (IgT) and other immune-relevant genes are common drawback effects of plant-based diets in gilthead sea bream (Calduch-Giner et al., 2012; Pérez-Sánchez et al., 2013; Piazzon et al., 2016). This is known to be associated with a pro-inflammatory condition, with loss of integrity and functionality of the epithelial intestinal barrier (Estensoro et al., 2016; Piazzon et al., 2017). However, most of these nutritionally-mediated effects, including changes in the sex proportion ratio, can be reversed by dietary sodium butyrate supplementation, resulting in a low male-female sex reversal and improved diseases outcomes in fish challenged with bacteria or myxozoan parasites (Piazzon et al., 2017; Simó-Mirabet et al., 2018a). It remains unclear if such results hold true for fish with different genetic backgrounds. In particular, it is not known if fast-growing selected gilthead sea bream differs in the utilization of diets with high or low FM/FO content, as genotype by diet (G × D) interactions have been widely reported from fly (Reed et al., 2010) to humans (Heianza and Qi, 2017). In fact, some carnivorous fish genotypes appear more suited to deal with plant-based diets than others, though most of these reports are restricted to salmonids (Pierce et al., 2008; Dupont-Nivet et al., 2009; Le Boucher et al., 2011a; Le Boucher et al., 2012; Yamamoto et al., 2015; Callet et al., 2017) and the European sea bass (Le Boucher et al., 2011b).

In gilthead sea bream, a major goal of genetic selection is the improvement of growth rates and feed conversion, though other important productive traits such as mortality rates, skeletal deformities, disease resistance, fillet yield, and flesh and carcass quality have been also evaluated (Navarro et al., 2009; Lee-Montero et al., 2015; García-Celdrán et al., 2015a, 2015b, 2015c; García-Celdrán et al., 2016; Janssen et al., 2017, 2018). However, most breeding programs only evaluate productive traits at harvest and, thereby, they can omit different growth trajectories or intermediate physiological states of relevance for other traits. For instance, penguin chicks (Geiger et al., 2012) and amphibian tadpoles (Gomez-Mestre et al., 2013) exhibit higher-than-normal growth to compensate growth breaks during winter or pond drying, resulting in increased risk of oxidative stress during catch-up growth periods. Certainly, a meta-analysis of growth performance across eight taxonomic classes reveals a close association between growth trajectories and oxidative stress (Smith et al., 2016), but the effects of growth selection on growth trajectories remain poorly studied in fish and other livestock animals. Therefore, the present gilthead sea bream study had a double aim: i) to determine if slow- or fast-growing fish show different growth trajectories over the production cycle and ii) to elucidate, at a pilot scale, any potential genome by diet interactions (G × D) in fish fed diets with graded levels of FM/FO replacement. To do that, genetically distinct fish were grown communally under the same environmental conditions with two contrasted diets. The study was limited to 16 full- and half-sibling families with divergent phenotypes, coming from the PROGENSA (Afonso et al., 2012) broodstock. Such approach ensured a relatively high genetic and phenotypic variability, in combination with a relatively high number of fish per family and diet. This design would allow high result robustness for growth-related traits, as reported in previous studies of genetic selection for improved utilization of plant-based diets in rainbow trout (Sadoul et al., 2016; Callet et al., 2018; Zhu et al., 2019).

2. Materials and methods

2.1. Ethics

All procedures were carried out according to IFAPA, IEO and IATS-CSIC Review Boards, European (2010/63/EU) animal directives and Spanish laws (Royal Decree RD53/2013) on the handling of experimental animals.

2.2. Experimental diets

Two extruded diets at a range of pellet sizes (1.5, 1.9, 3, 4.5 mm) were formulated and produced by BioMar (BioMar Process Innovation Technical Centre, Brande, Denmark), on the basis of feeds of the ARRAINA EU project (Benedito-Palos et al., 2016). Diets were isonitrogenous, isolipidic and isoenergetic, and met all known nutritional requirements of gilthead sea bream. Marine meals were included at 25% in the D1 (control) diet and at 5% in the D2 diet. Added FO was 14.1% for D1 diet and 3.9% for D2 diet, decreasing EPA + DHA content from 3.8 to 1.2%. Lysine, methionine, lecithin and monocalcium phosphate were balanced in D2 diet to the values of D1 diet. Composition of experimental diets is shown in Table 1.

2.3. Broodstock crosses

To produce slow- (c_xc_y) and fast- (e_xe_y) growing families, fish breeders belonging to the Spanish selection program of gilthead sea bream (PROGENSA) (García-Celdrán et al., 2015a; García-Celdrán et al., 2016; Lee-Montero et al., 2015) were used. These fish were hosted at IFAPA El Toruño (El Puerto de Santa María, Spain). The PROGENSA broodstock rendering slow growing fish was composed of 52 non-selected animals after two rounds of selection (generation 2). The PROGENSA broodstock rendering fast growing fish was composed of 23 selected females from G1 and 7 selected males from G2. In November 2016, the two broodstocks were moved to spawning tanks to synchronize egg production under controlled photoperiod (8D:16 L) and non-restricted feeding (Vitalis CAL-9, Skretting, Burgos, Spain). In March 2017, all breeders were anesthetized (200 ppm phenoxyethanol) and sexed. Then, nine (3 females, 6 males) and six (3 females and 3 males) fish with estimated breeding value for length of -0.9 ± 0.2 cm and $+0.9 \pm 0.7$ cm, respectively, were selected and moved to two new tanks to produce familial crosses. Spawns occurred immediately after the formation of these two mini-broodstocks. Two spawns (one from low estimated breeding value broodstock and one from high estimated breeding value broodstock) with > 150.000 floating eggs, corresponding to three consecutive days taken in two consecutive weeks, were collected and incubated separately (20 °C, 35‰ salinity) in cylinder conical tanks (400 L). When all larvae were hatched at 24 h, 100,000 larvae of each group were sent to the hatchery of IEO in Murcia.

Table 1
Ingredients and chemical composition of experimental diets.

Ingredient (%)	D1	D2
Fish meal	23.0	3.0
Fish hydrolysate (CPSP)	2.0	2.0
Soya protein	16.7	25.6
Corn gluten	16.5	25.5
Wheat gluten	4.5	7.3
Rapeseed cake	12	10
Wheat	10	7.4
Fish oil	14.1	3.9
Rapeseed oil	0	9
Mineral-vitamin mix[a]	1.25	6.3
Proximate composition (%)		
Moisture	7.9	7.5
Crude protein	45	45
Crude fat	20.1	20.1
Ash	6.9	5.9
NFE[b]	19.1	19.8
ARA[c]	0.17	0.05
EPA[d]	2.30	0.60
DHA[e]	1.50	0.42
EPA + DHA	3.8	1.02
Crude energy (MJ/kg)	22.1	22.3

[a] Contains vitamins, minerals, amino acids, cholesterol, lecithin and antioxidants.
[b] Nitrogen free extract.
[c] Arachidonic acid (20:4n-6).
[d] Eicosapentaenoic acid (20:5n-3).
[e] Docosahexaenoic acid (20:6n-3).

2.4. Larval rearing, weaning, and pre-fattening

Larval rearing was conducted under standard conditions at 18.5 °C with feeding started on live preys once the mouth was opened at 4 days post-hatching (dph). Larvae were successively fed with enriched (Selco, Inve Animal Health) rotifers from 4 to 22 dph, *Artemia* nauplii (Inve Animal Health) from 18 to 25 dph, enriched Instar II *Artemia* from 23 to 50 dph and a commercial diet (Gemma Wean, Skretting) from 23 dph onward. At 73–77 dph (June 2017), c_xc_y and e_xe_y offsprings (80–120 mg) were transported to the experimental growth facilities of the Nutrigenomics Group at IATS-CSIC in Castellón. Upon arrival, fish were kept in a recirculating aquaculture system (RAS) of six 500 L tanks under highly controlled conditions (initial density 3 fish/L, salinity 38‰, temperature 18-19 °oC, water oxygen 6–7 ppm, and ammonia concentration < 0.1 mg/L). At 3–6 g of body weight (BW), fish were transferred to a flow-through system under the natural photoperiod and water temperature at IATS latitude (40° 5′N; 0° 10′E). During this initial growing period, fish were fed with commercial diets according to their size (0.2–0.3 mm, Skretting Gemma Wean; 0.5 mm, Skretting Gemma Wean Diamond; 0.8 mm Skretting Perla Plus 2.0; 1.5 mm Biomar Intro Plus MT).

2.5. Long-term feeding trial

At ~180 dph (September 2017), 2545 fish were individually tagged (dorsal muscle) with passive integrated transponders (PIT) (ID-100A 1.25 Nano Transponder, Trovan), being the progeny of each group randomly and equally distributed into 3000 L tanks under natural photoperiod and temperature conditions. Water oxygen levels were always higher than 5.6 ppm, and fish density varied from 2.5 Kg/m^3 at the beginning to 12 Kg/m^3 at the end of the 12-month feeding trial (September 2017–September 2018). Over the first three weeks, fish were fed with a mix (1:1) of D1 and D2 at the smallest pellet size (1.5 mm). Then, each diet was randomly allocated to three tanks. The fish from each group were later moved through the experimental period in two additional tanks per diet (final total: 5 tanks/diet). All replicates conserved the same amount of fish and family composition throughout

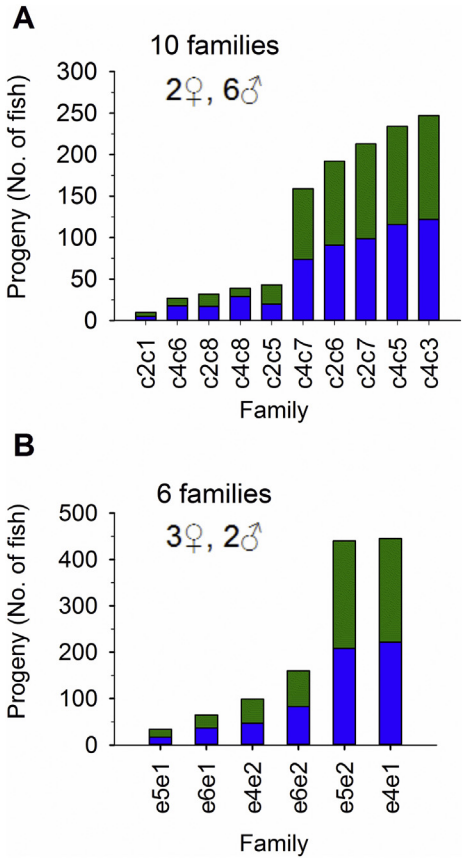

Fig. 1. Family composition and number of fish allocated to each experimental diet (D1; lower half of bars; D2, upper half of bars). Slow-growing (c_xc_y) (A) and fast-growing (e_xe_y) (B) families. Parents are defined as × subscript for female and y subscript for male.

the experimental period, with a similar number of family members allocated to each dietary treatment (Fig. 1). For fish genotyping (see Section 2.6), a portion of caudal fin from each fish was clipped and stored individually in RNA later for parents assignments. In April 2018, fish that could not be unequivocally assigned to a pair of parents were removed from the experiment. Feed intake was recorded weekly and no significant mortalities occurred during the trial. Fish were wet-weighed and their standard length was measured at initial (September 2017), intermediate (November 2017, April 2018, May 2018, July 2018, August 2018) and final (September 2018) sampling points, using a FR-200 FishReader W (Trovan, Madrid, Spain) for data capture and pre-processing. Over the course of the trial, fish were fed by automatic feeders 1–2 times per day and 3–7 days per week according to fish size and season, being the ration adjusted weekly to a level close to satiation.

2.6. Genotyping and pedigree reconstruction

DNA from fins was extracted using the BioSprint 96 DNA Blood Kit (QIAGEN®) operated by a Biosprint 96 robot. The concentration of extracted DNA was measured using a NanoDrop 8000 spectrophotometer v.3.7 (Thermo Fisher Scientific) and normalized to 80 ng/μL prior to PCR amplification. PCR reactions were carried out by means of a TECAN robot Freedom Evo (Tecan Schweiz AG, Switzerland) and the Freedom Evowar® Standard v.2.5 software following the manufacturer's instructions. Breeders and offspring were genotypically characterized by a SMsa1 multiplex PCR containing 11 specific microsatellite markers (Lee-Montero et al., 2013). Genotypes were determined by GENEMAPPER v.3.7 software (Life Technologies®). Family relationships were determined by the exclusion method using

Table 2
Growth performance of gilthead sea bream juveniles fed the experimental diets (D1, D2) from September 2017 to September 2018. Values of each feeding regime for all fish population are the mean ± sem (3–5 replicate tanks).

Diet	Mean body weight (g)		SGR[a] (%)	CF[b]	Feed intake	FE[c]
	Initial	Final			(g dry feed/fish)	
Week 7, 26th September 2017-14th November 2017						
D1(FM25/FO14)	17.18 ± 0.17	42.36 ± 1.01	1.86 ± 0.02	2.70 ± 0.01	24.96 ± 0.93	1.02 ± 0.04
D2(FM5/FO4)	17.20 ± 0.01	41.38 ± 0.17	1.79 ± 0.01	2.73 ± 0.01	24.43 ± 0.16	0.99 ± 0.01
Week 27,15th November 2017-3th April 2018						
D1(FM25/FO14)	42.36 ± 1.01	56.34 ± 0.94	0.21 ± 0.01	2.53 ± 0.01	24.59 ± 0.04	0.57 ± 0.01
D2(FM5/FO4)	41.38 ± 0.17	55.13 ± 0.55	0.21 ± 0.004	2.54 ± 0.01	25.48 ± 0.31	0.54 ± 0.001
Week 35, 4th April 2018-30th May 2018						
D1(FM25/FO14)	56.34 ± 0.94	71.87 ± 1.30	0.45 ± 0.01	2.49 ± 0.03	21.02 ± 0.11	0.74 ± 0.03
D2(FM5/FO4)	55.13 ± 0.55	69.48 ± 0.09	0.43 ± 0.02	2.46 ± 0.01	21.21 ± 0.28	0.68 ± 0.02
Week 44, 31th May 2018-30th July 2018						
D1(FM25/FO14)	71.76 ± 0.70	137.67 ± 0.58	1.09 ± 0.02	2.58 ± 0.004	75.75 ± 1.05	0.87 ± 0.01
D2(FM5/FO4)	69.43 ± 0.05	129.75 ± 1.11	1.04 ± 0.02	2.60 ± 0.01	71.38 ± 1.38	0.84 ± 0.01
Week 51, 31th July 2018- 17th September 2018						
D1(FM25/FO14)	137.99 ± 0.87	217.42 ± 2.54	0.96 ± 0.01	2.99 ± 0.18	94.23 ± 0.98	0.85 ± 0.01
D2(FM5/FO4)	129.17 ± 1.26	209.10 ± 2.21	1.00 ± 0.01	2.92 ± 0.01	93.01 ± 0.75	0.86 ± 0.01
Overall September 2017–September 2018						
D1(FM25/FO14)	17.18 ± 0.17	217.4 ± 2.54	0.71 ± 0.003	2.99 ± 0.18	263.4 ± 1.34	0.76 ± 0.006
D2(FM5/FO2.5)	17.20 ± 0.01	209.1 ± 2.21	0.70 ± 0.003	2.92 ± 0.01	256.9 ± 4.14	0.75 ± 0.002

[a] Specific growth rate, SGR = 100 × (ln final body weight – ln initial body weight)/days.
[b] Condition factor, CF = 100 × (body weight/standard length^3).
[c] Feed efficiency, FE = 100 × (wet weight gain/dry feed intake).

VITASSIGN (v8.2.1) software (Vandeputte et al., 2006). For simplicity, we refer to both full- and half-sibling fish as a 'family'.

2.7. Morphometric features of selected families with differences in growth trajectory

Five families were selected as representative of the population on the basis of their growth rates from September 2017 to April 2018, taking also into account their parents origin and offspring contribution. This progeny subset included 2 families (c2c7, c4c3) from the low estimated breeding value broodstock and exhibited slow growth rates. The other 3 families (e4e1, e5e2, e6e2) originated from the high estimated breeding value broodstock and exhibited intermediate (e4e1) or fast (e5e2, e6e2) growth. Randomly selected fish from these families were sampled in July 2018 for the calculation of organo-somatic indexes as ratios of body weight (hepatosomatic index, HSI; mesenteric fat index, MSI; intestinal weight index, IWI), or standard length (intestinal length index, ILI). In addition, blood and tissue samples from liver, skeletal muscle, adipose tissue and intestine were freshly preprocessed or frozen in liquid nitrogen prior storage at −80 °C for posterior biochemical, histological, transcriptomic and metagenomics analyses.

2.8. Statistical analysis

Statistical analyses were done using SPSS Statistics for Windows v.24 (IBM Corp., Armonk, N.Y., USA) with all *P*-values set to 0.05. Normality and equal variance of data were tested by Shapiro-Wilk and Levene tests, respectively. To examine the similarity of initial family distribution among experimental tanks, the chi-square (χ^2) test was performed. Growth parameters of each dietary group as a whole were analyzed by Student *t*-tests. Regression and Pearson correlation analyses were used to describe the growth performance of each family on both diets, and to gain insights into G × D interactions. To further analyze G × D interactions, a general linear mixed model was developed including all possible fixed and random effects and their (two-way) interactions. Then, a backward selection of the best fitting model was performed following the Akaike information criterion (AIC). The final model was: $y_{ijkl} = \mu + G_i + D_j + (GxD)_{ij} + T_{k(j)} + ßxBW_l + \varepsilon_{ijkl}$, where y_{ijkl} is the phenotypic value of individual SGR, μ is the overall mean, G_i is the genotype (family) fixed effect, D_j is the diet fixed effect, GxD_{ij} is the genotype × diet interaction, $T_{k(j)}$ is the random tank effect nested within diet, $ß$ is the regression coefficient of initial body weight (BW) included as a covariate, and ε_{ijkl} is the model error. Growth and tissue biometric data from representative families of the total population were processed by two-way ANOVA followed by the Tukey test.

3. Results

3.1. Parentage assignment and family's distribution

Up to 2441 individuals (96% population) were genotyped and unequivocally assigned to a single pair of parents, resulting in 18 families with the contribution of two females and six males for c_xc_y families, and three females and two males for e_xe_y families. Two families were only represented by one individual and they were discarded from the study, which was then reduced to 16 families with a similar representation in each replicate tank ($\chi^2 = 81.65$, $P = 0.280$), and equally fed D1 and D2 diets (Fig. 1). Five families (c2c1, c2c8, c4c6, c4c8, e5e1) were represented by < 20 fish/diet and they were considered in the analysis of the overall growth by diet, but excluded from G × D interaction analysis that was finally performed with six c_xc_y families (c2c5, c2c6, c2c7, c4c3, c4c5, c4c7) and five e_xe_y families (e4e1, e4e2, e5e2, e6e1, e6e2).

3.2. Growth performance by diet

Data on growth performance, considering together all fish families under each dietary condition, are shown in Table 2 and Fig. 2. No differences in specific growth rate (SGR) between both dietary treatments were observed. SGR decreased from 1.8 in September 2017–November 2017 to 0.21 during the cold period (November 2017–April 2018), but increased again during the spring-summer period of 2018, with an SGR close to 1 from May 2018 to September 2018. Feed efficiency (FE) remained similar for the two dietary groups with values ranging from 1.02–0.99 during September 2017-Novembre 2017 and 0.57–0.54 during the cold period. This yielded an overall SGR

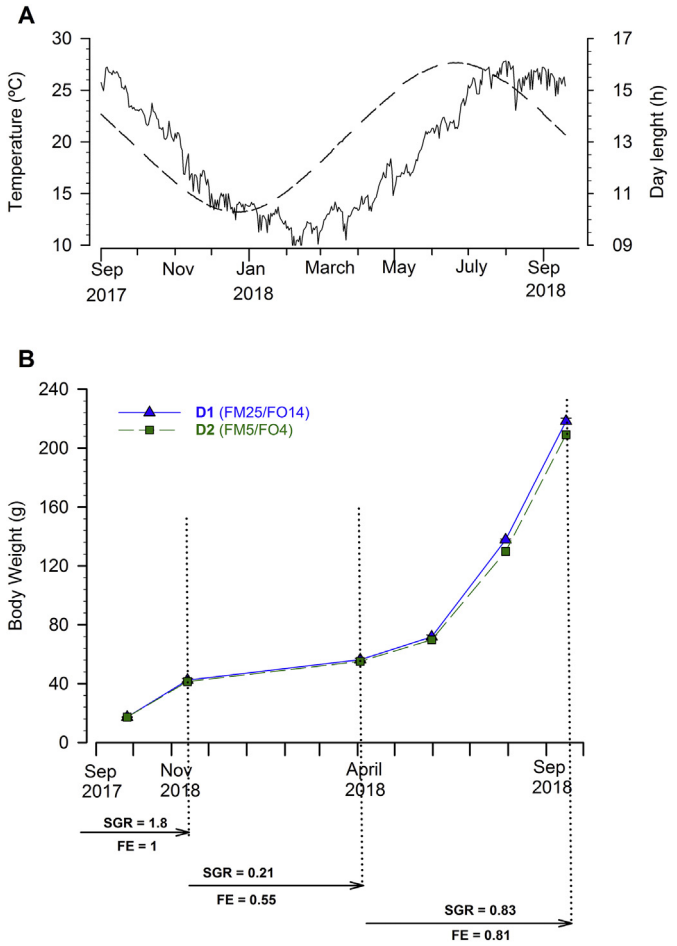

Fig. 2. Seasonal changes in temperature (solid line) and day length (dotted line) during the feeding trial (A). Body weight, specific growth rates (SGR) and feed efficiency (FE) of juvenile fish fed the two experimental diets (D1, D2). Values of each feeding regimen for all fish population are the mean ± sem of 3–5 replicates.

of 0.7 and an overall FE of 0.75–0.76, which was unaltered by dietary treatment. Condition factor (CF) also remained unaltered by dietary treatment, varying cyclically from 2.4 to 2.9 with the increase of feed intake and fish size (Table 2).

3.3. Family's growth performance

In Fig. 3, the evolution of BW and CF over the entire trial is shown for each family, with no distinction of dietary regimen. As a general rule, e_xe_y offspring grew faster than c_xc_y offspring from September 2017 to November 2017 (Fig. 3A, B). This fast-growing families continued growing faster until May 2018 (Fig. 3C, D), and the highest differentiation between e_xe_y and c_xc_y families in terms of BW and CF was achieved in April–May 2018, just before the summer growth spurt. During the second-half of the trial (May 2018–September 2018), the c_xc_y offspring grew at the same rate, or even faster, than its e_xe_y counterpart. This growth improvement minimized the differences in CF among families, though it was not enough to completely avoid differences in final BW (September 2018) (Fig. 3E, F). Hence, regardless of dietary treatment, frequency histograms of BW at initial (Fig. 4A, D), intermediate (Fig. 4B, E) and final (Fig. 4C, F) sampling points highlighted a maximum separation of the two populations in May 2018, with less separation along x-axis at the end of trial (September 2018).

3.4. G × D interaction

The G × D interaction on growth rate was first assessed by regression and correlation analyses of SGRs on each dietary condition. The scatterplot of SGRs of each family and nutritional condition highlighted a close linear relationship ($R^2 = 0.99$), with a slope equal to 1.01. This finding indicates that each family grew at the same rate on both diets over all the experimental period (Fig. 5A). When the analysis was reduced to families with the higher offspring contribution (> 50 fish per family), the SGR scatterplot for the first-half of the trial (September 2017–May 2018) revealed a significant phenotypic correlation ($R = 0.94$, $F = 66.9$, $P < 0.001$), moving e_xe_y families towards the right of x-axis (Fig. 5B). At the end of trial, the same trend was evidenced for overall SGRs ($R = 0.77$, $F = 13.5$, $P = 0.005$), though the differentiation between c_xc_y and e_xe_y families was slightly buried due to the enhanced growth of c_xc_y offspring after overwintering (Fig. 5C). These high phenotypic correlations suggest that genetic variation accounts for most of the observed growth variability, being weak the G × D interaction. The strong effect of the genotype and the poor relevance of interaction on growth rate were further supported by reaction norms for SGR across diets during the first half and the entire trial, resulting in a poor SGR re-ranking of families (Fig. 6). This observation also agreed with the results obtained by the general linear mixed model, which revealed a strong effect of genotype ($df = 10$, $F = 14.16$, $P < 0.0001$), but not of diet ($df = 1$, $F = 2.75$, $P = 0.14$), despite of a statistically significant G × D interaction ($df = 10$, $F = 2.49$, $P < 0.01$).

3.5. Biometric indexes

Biometric data from randomly selected fish (20 fish per family and dietary condition) of five families, representative of the entire population, are shown in Table 3. Fish from c2c7 and c4c3 families exhibited low SGR. Fish from e4e2, e5e2 and e6e2 families differed in growth rates, with intermediate (e4e2) and high (e5e2 and e6e2) SGR values. As expected, a family (genotype) effect was found for BW, standard length and CF, but diet effects and G × D interactions were not found. Liver and fat weight, as well as HSI and MSI, were affected by both the genotype and the diet, but without G × D interaction. D1 group fish exhibited lower HSI and higher MSI than fish from D2 group. The lower HSI within each dietary group was exhibited by fast growing families, whereas the highest MSI was observed in the least growing family (c4c3). The intestinal features ILI and IWI were affected by diet, with higher values in D2 fish, but without an effect of the genotype or G × D interaction. However, a clear pattern was depicted when families were grouped phenotypically as groups of low (c2c7, c4c3), medium (e4e1) and high (e5e2, e6e2) growth rates (Fig. 7). This clustering highlights the shorter intestine of fast growing families, with intermediate ILI values for e4e1 when fish fed D1 (Fig. 7A). However, ILI values of all fish groups remained almost equal when feeding D2 (Fig. 7B).

4. Discussion

Low FM and FO diets based on plant products are able to support high growth rates in gilthead sea bream (De Francesco et al., 2007; Monge-Ortiz et al., 2016; Benedito-Palos et al., 2016; Simó-Mirabet et al., 2018a), and the present study revealed that this holds true for fish with different genetic background from the PROGENSA broodstock. Over the course of the winter period, the FE of the whole fish population felt to 0.5 on both diets, increasing up to 0.8–1 during active feeding periods. The decrease in FE during winter might be related with previously reported muscle UCP3-mediated metabolic inefficiency during winter in gilthead sea bream (Bermejo-Nogales et al., 2010), although other factors may also contribute such as decreased diet digestibility, the energy cost of increasing in size and performed lipogenesis, coupled with weight growth stagnant and loss of fat depots during this season. Overall SGRs are difficult to compare with previous

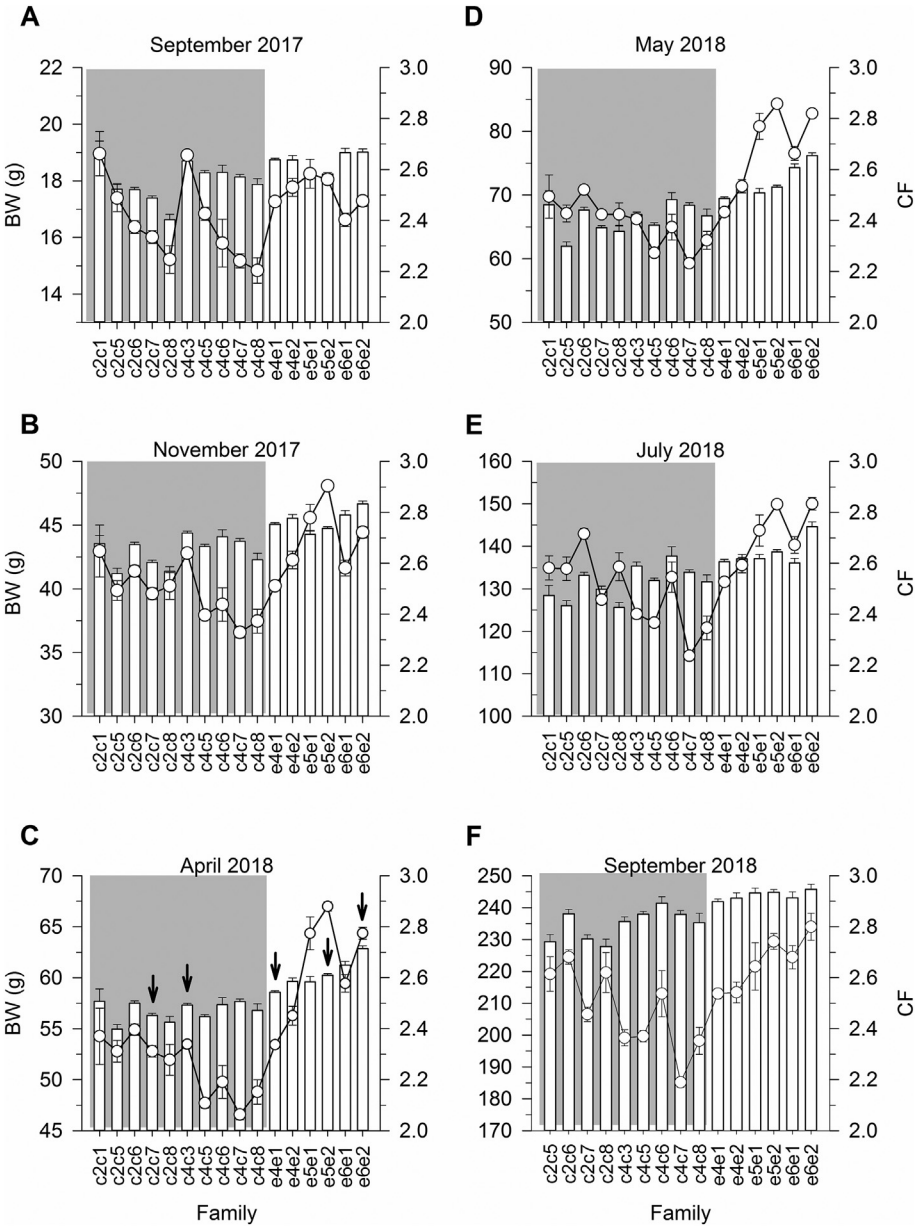

Fig. 3. Body weight (BW, lines) and condition factor (CF, columns) of slow-growing (c_xc_y, grey background) and fast-growing (e_xe_y, white background) families over the course of the feeding trial from September 2017 (A) to September 2018 (F). Data from the two feeding regimes were combined and each family value are the mean ± sem of all fish in each family. Arrowheads indicate the families selected for tissue biometric indexes, covering growth rates from low to high.

long-term trials because of the high impact of the stocking time on the productive yield of animals with pronounced growth seasonality. The final weight of fish in the present study was slightly lower than that achieved in our experimental facilities, at a similar stocking time, by a fast growing strain of Atlantic origin (Mingarro et al., 2002). However, it is noteworthy that the commercial fish line used in that study was already selected for growth, whereas the population tested herein included fish with both fast and intended slow growth. In spite of this, the two tested diets would meet the nutrient requirements for growth, as high overall FE was achieved with both diets despite the intermediate growth-stunted winter season. The advantage of such extended grow-out period (autumn instead of spring stocking time) is that it makes more feasible the pedigree reconstruction over the course of the feeding trial, facilitating the selection of families and individuals for tissue sampling and ongoing swimming tests and parasite challenges.

As expected, the e_xe_y offspring grew faster than c_xc_y offspring. This was not surprising as both populations were shaped through genetic selection and structured by estimated breeding values (Afonso et al., 2012). Interestingly, we found different seasonal growth rates between populations. Until May 2018, the fast-growing group attained a mean BW 15% higher than the slow-growing population (BW: 77 vs. 65 g). Among individual families, the fastest growing family grew 22% faster than the low-growing population (BW: 83 vs. 65 g) and 28% faster than the least growing family (BW: 83 vs. 59 g). However, these differences were reduced at the end of the trial (September 2018); the difference between populations decreased from 15% to 8%, the difference between the fastest growing family and the slow-growing population fell from 22% to 13%, and the difference between the fastest and the least growing family fell from 28% to 21%. Therefore, selected fish grew faster during the first growth spurt and overwintering, whereas most families from the low estimated breeding value broodstock showed the strongest growth arrest during the cold season, but thereafter they exhibited the highest compensatory growth (i.e., accelerated growth following growth-stunting conditions, Quinton and Blake, 1990; Kim and

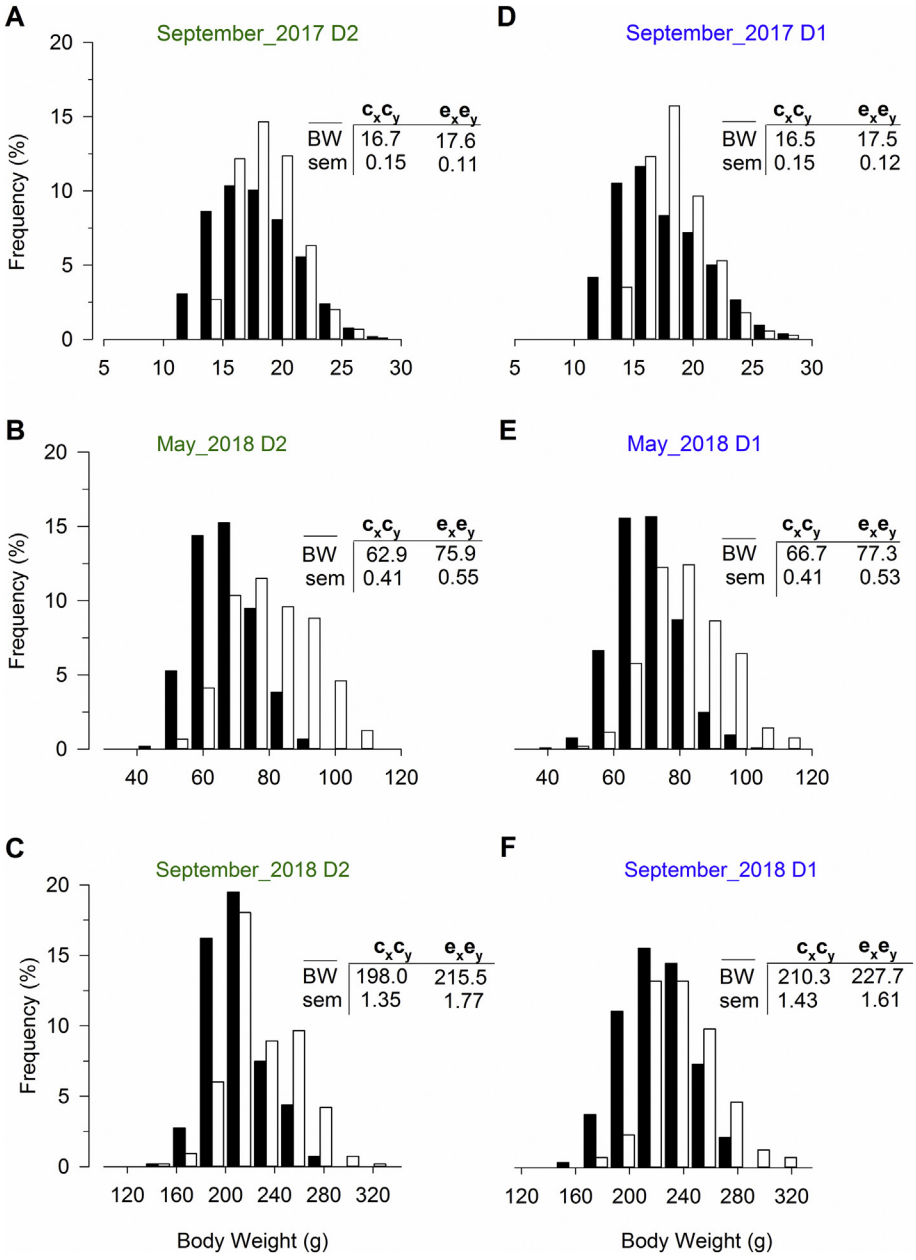

Fig. 4. Frequency distribution of body weight (BW) of slow-growing (S, black bars) and fast-growing (F, white bars) fish families at initial (A, D), intermediate (B, E) and final (C, F) sampling points through the feeding trial. Average BW and sem are indicated for the two family groups on each dietary condition. Fish fed D1 on the left; fish fed D2 on the right.

Lovell, 1995; Won and Borski, 2013). It can be speculated that this convergence over time would be favored under highly controlled laboratory conditions, whereas compensatory growth during the latter stages of fish farming would be more complicated at the farm level, due to logistic constraints to highly increase feeding at a precise period of the production cycle. Indeed, selection for shaping these populations was performed at harvest under realistic farming conditions and, which included two winter seasons. Thus, it is possible that the selection process had favored a lower impact of overwintering on growth rates.

According to the lipostatic theory of feed intake, selection for a more continuous growth would prime leaner fish, which eat more and grow faster than their fatter counterparts (Jobling and Johansen, 1999; Johansen et al., 2002). Certainly, enhanced feed intake is considered the most important factor behind the genetically improved growth in trout (Callet et al., 2017). In our experimental setup, individual or family measures of feed intake were not feasible, though the close positive association of CF and growth rates supports a strong family effect on feed intake and growth trajectories. Likewise, in common carp, fish which grew or lost less weight while overwintering achieved higher BW during the subsequent growing period (Prchal et al., 2018). Fish show a particularly robust capacity for catch-up growth (Won and Borski, 2013), though controversial results have been reported in gilthead sea bream, as fish subjected to restricted feeding were often unable to completely catch-up BW or body length during the subsequent satiation feeding period (Şahin et al., 2000; Eroldoğan et al., 2008; Bavčević et al., 2010; Peres et al., 2011). If this feature is potentiated by a particular genetic background or any other unknown factor remains to be solved, as it might also reflect different susceptibilities to oxidative stress, pathogen exposure or other stressful conditions.

Different studies in rainbow trout have found significant G × D interactions in fish fed diets with a very high level of FM replacement (Pierce et al., 2008) or a total substitution of marine ingredients by

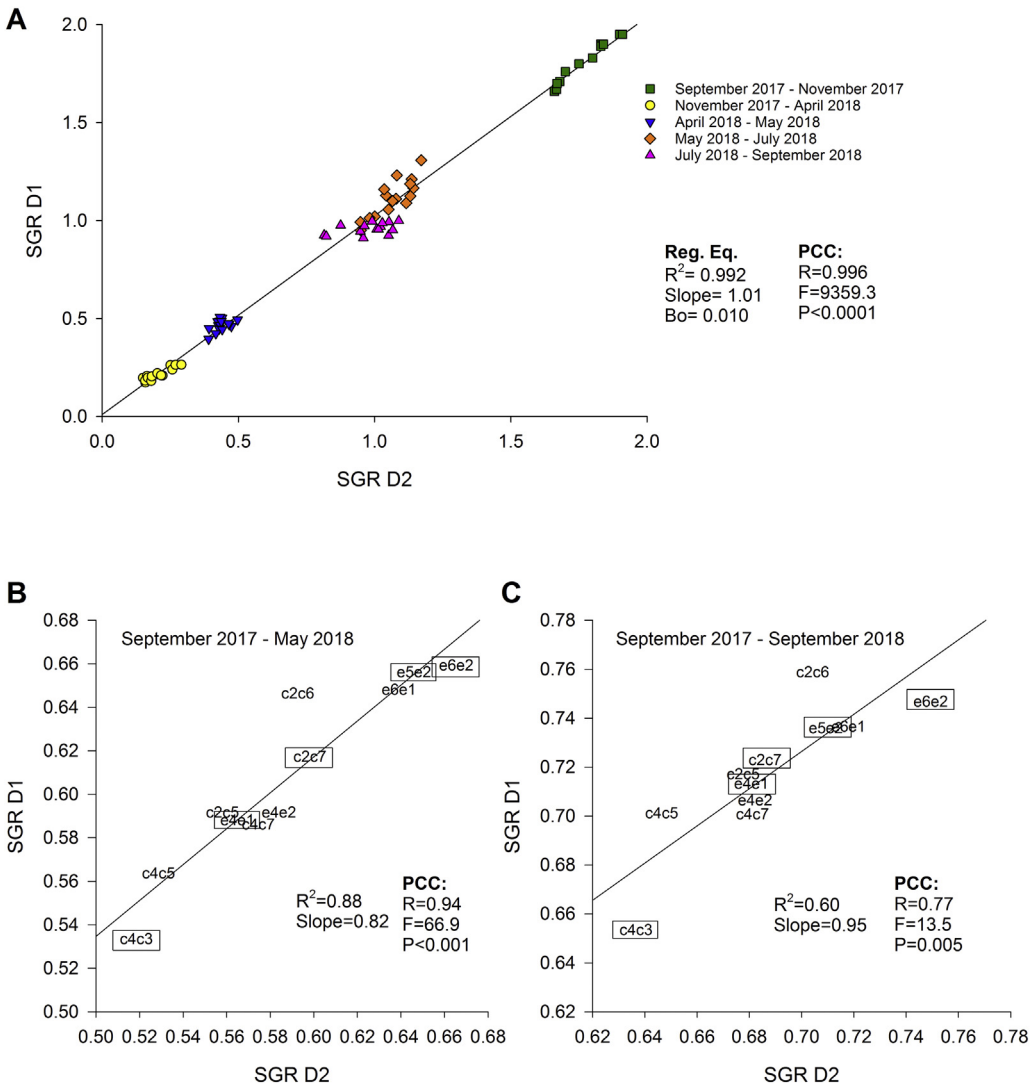

Fig. 5. Specific growth rates (SGR) of slow-growing (c_xc_y) and fast-growing (e_xe_y) fish families fed experimental diets (D1, D2). Data on regression equation (Reg. eq.) and Pearson correlation coefficient (PCC) are provided for data covering all discrete periods (A). The same analysis is reported following overwintering (B) and at the end of trial (C). Squares indicate families selected for morphometric analysis, covering the SGR range from low to high.

plant products (Le Boucher et al., 2011a). Thus, survival and growth rates are improved in trout after a single generation of selection for the ability to adapt to a totally plant-based diet (Le Boucher et al., 2012). Moreover, after few generations, both trout and amago salmon are able to grow on low FM diets at the same rate than control lines fed standard diets (Yamamoto et al., 2015; Callet et al., 2017). In the European sea bass, significant G × D interactions have also been reported for different growth and productive traits when fish were fed FM/FO free diets (Le Boucher et al., 2013). However, this interaction was weak and the authors concluded that genetic selection of fish for growth on a marine diet should be the most efficient way to increase growth on plant-based diets. Collectively, our results suggest that this would also be the case of gilthead sea bream, though we found a significant G × D interaction by the general linear mixed model. However, the high phenotypic correlations observed for SGRs across families on both diets (0.94 until May 2008 and 0.77 for the one-year trial) indicate that this interaction was weak. Indeed, genotype by environment (G × E) interactions in fish, and gilthead sea bream in particular, are considered irrelevant when genotypic correlations of a trait are higher than 0.6–0.7 (Navarro et al., 2009; Sae-Lim et al., 2013; Lee-Montero et al., 2015). We did not attempt to obtain genetic correlations because a higher number of families are needed to estimate this parameter with accuracy (Cheverud, 1988; Sae-Lim et al., 2010, 2016). However, phenotypic correlations are fair estimates of their genetic counterparts (Cheverud, 1988; Reusch and Blanckenhorn, 1998; Sodini et al., 2018), particularly for traits related to growth (Hadfield et al., 2007). This means that growth is perhaps a genetic character with a limited G × D interaction with the practice of a gradual replacement of both marine FM and FO by alternative ingredients in feeds formulated to avoid nutritional deficiencies or anti-nutritional factors. The poor relevance of this interaction was further supported by reaction norms for SGR across diets, showing poor re-ranking of families, with most differences between genotypes being of scale (slightly different slopes). Certainly, a quantitative review across 38 species showed that G × E interactions are lacking for many economically important traits, being re-ranking moderate for growth and survival (Sae-Lim et al., 2016). Herein, this feature would be favored by the use of a well-balanced plant diet formulation, which does not limit the maximum growth of gilthead sea bream (Simó-Mirabet et al., 2018a). This idea is supported by the same growth performance of the whole population fed the experimental diets, and the lack of a main effect of diet on family's SGRs as revealed by the general linear mixed model.

In contrast to growth traits, organosomatic indexes were affected by both diet and genotype. Gut length is the result of a trade-off between

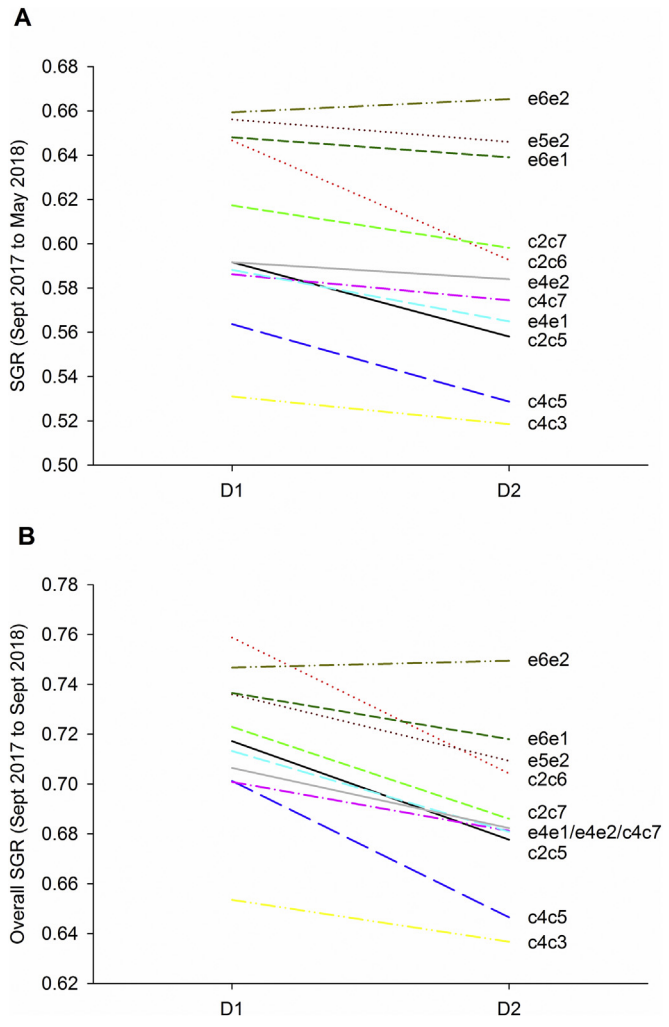

Fig. 6. Reaction norm for SGR across experimental diets (D1 and D2) during the first half (A) and during all the trial (B). Only family c2c6 exhibited evident re-ranking while most differences between genotypes are of scale (slightly different slopes). Differences in overall SGR (B) between diets fall within the very narrow range of 0.64–0.76 for all families in the study, including c2c6.

maximum nutrient absorption and minimum cost of maintenance (Zandonà et al., 2015), and we found herein that gilthead sea bream had the capacity to adapt to the changing diet by enlarging their intestines and, thereby, increasing their digestive/absorptive capacity. The plasticity of intestine length has been reported elsewhere in gilthead sea bream (Santigosa et al., 2008; Simó-Mirabet et al., 2017) and other farmed fish (Olsson et al., 2007; Santigosa et al., 2008; Zandonà et al., 2015). For instance, *Bacillus*-based probiotics induced higher intestinal folds and shorter intestines in fast growing gilthead sea bream (Simó-Mirabet et al., 2017), whereas 50% of FM replacement by plant proteins was associated with an increase in intestinal length, though the latter did not preclude growth impairment (Santigosa et al., 2008). This was not the case of the present study, and the enlarged intestine of fish fed the challenging plant-based diet is viewed as an effective adaptive mechanism to preserve maximum growth. Interestingly, this intestinal plasticity was genetically regulated, and fast growing families (e.g., e5e2, e6e2) had shorter intestines when fed D1, but they exhibited enlarged intestines when fed D2. This result agrees with the notion that the intestine is a key target tissue for improved growth and welfare in most farmed fish (Estensoro et al., 2016; Piazzon et al., 2017; Torrecillas et al., 2016, 2017). Accordingly, ongoing studies aim to assess how changes on intestinal morphometrics (nutritionally and genetically regulated) correlate with changes in gut microbiota

Table 3
Biometric and organosomatic indexes of juvenile fish from slow-growing (c2c7, c4c3) and fast-growing families (e4e1, e5e2, e6e2) fed experimental diets (D1, D2). Values are mean ± sem, at July sampling time, of 20 fish (BW, standard length, CF, liver weight, mesenteric fat weight, HSI, MSI) and 8 fish (intestinal weight index, IWI; intestinal length index, ILI). The results of 2-way ANOVA are shown as *P*-values for each main factor (family and diet) and their interaction. Different letters in the same row indicate statistically significant differences (Tukey test, $P < 0.05$).

	D1					D2					P-value (2-way ANOVA)		
	c2c7	c4c3	e4e1	e5e2	e6e2	c2c7	c4c3	e4e1	e5e2	e6e2	Family	Diet	Interaction
Body weight (g)	133.2b ± 2.02	126.0b ± 2.42	134.1b ± 2.63	147.3a ± 3.56	149.1a ± 3.22	123.4b ± 4.08	124.0b ± 2.18	129.5b ± 4.32	146.1a ± 4.02	152.5a ± 3.97	**< 0.001**	0.183	0.382
Standard length (cm)	17.27ab ± 0.123	16.82b ± 0.172	16.93b ± 0.153	17.41a ± 0.190	17.35a ± 0.205	16.68b ± 0.179	16.54b ± 0.109	16.71b ± 0.236	17.37a ± 0.169	17.46a ± 0.169	**< 0.001**	0.066	0.316
Condition Factor[1]	2.59c ± 0.04	2.66bc ± 0.05	2.77b ± 0.04	2.79b ± 0.05	2.87a ± 0.07	2.65c ± 0.04	2.74bc ± 0.03	2.77b ± 0.03	2.78b ± 0.04	2.86a ± 0.04	**< 0.001**	0.367	0.721
Liver weight (g)	1.41a ± 0.04	1.28b ± 0.06	1.25b ± 0.04	1.31b ± 0.06	1.42a ± 0.08	1.55a ± 0.07	1.39b ± 0.05	1.30b ± 0.04	1.31b ± 0.07	1.55a ± 0.07	**< 0.001**	**0.027**	0.775
Mesenteric fat weight (g)	2.29b ± 0.28	3.13a ± 0.25	2.14b ± 0.16	2.63b ± 0.16	2.98a ± 0.24	1.42b ± 0.15	2.87a ± 0.24	1.74b ± 0.10	2.00b ± 0.19	2.33a ± 0.16	**< 0.001**	**< 0.001**	0.589
Intestine weight (g)	2.42ab ± 0.19	2.02b ± 0.19	2.24b ± 0.12	2.32ab ± 0.09	2.70a ± 0.15	2.39ab ± 0.13	2.37b ± 0.09	2.19b ± 0.20	2.74ab ± 0.12	2.92a ± 0.18	**< 0.001**	0.055	0.385
Intestine length (cm)	13.20 ± 1.12	11.57 ± 0.71	11.69 ± 0.87	11.60 ± 1.13	11.25 ± 1.05	14.12 ± 2.11	13.00 ± 1.33	14.53 ± 1.44	14.50 ± 0.69	12.46 ± 0.93	0.581	**0.017**	0.878
Hepatosomatic index[2]	1.06a ± 0.03	1.02ab ± 0.04	0.94bc ± 0.03	0.90c ± 0.05	0.95bc ± 0.05	1.25a ± 0.03	1.12ab ± 0.04	1.02bc ± 0.03	0.89c ± 0.04	1.02bc ± 0.04	**< 0.001**	**< 0.001**	0.168
Mesenteric fat index[3]	1.70b ± 0.20	2.49a ± 0.20	1.58b ± 0.11	1.78b ± 0.10	2.00b ± 0.16	1.14b ± 0.11	2.32a ± 0.20	1.36b ± 0.09	1.34b ± 0.11	1.51b ± 0.08	**< 0.001**	**< 0.001**	0.571
Intestinal weight index[4]	1.68 ± 0.11	1.53 ± 0.15	1.60 ± 0.06	1.51 ± 0.05	1.65 ± 0.09	1.89 ± 0.10	1.87 ± 0.07	1.57 ± 0.11	1.79 ± 0.07	1.87 ± 0.11	0.24	**0.001**	0.349
Intestinal length index[5]	75.1 ± 6.16	66.3 ± 3.99	63.2 ± 4.06	58.9 ± 4.47	56.7 ± 2.67	71.1 ± 5.39	77.0 ± 7.59	76.0 ± 6.73	81.00 ± 4.03	69.4 ± 5.29	0.372	**0.002**	0.194

Statistical differences appeared in bold

[1] CF = 100 × (body weight/standard length[3]).

[2] HSI = 100 × (liver weight/fish weight).

[3] MSI = 100 × (mesenteric fat weight/fish weight).

[4] IWI = 100 × (intestine weight/fish weight).

[5] ILI = 100 × (intestine length/standard length).

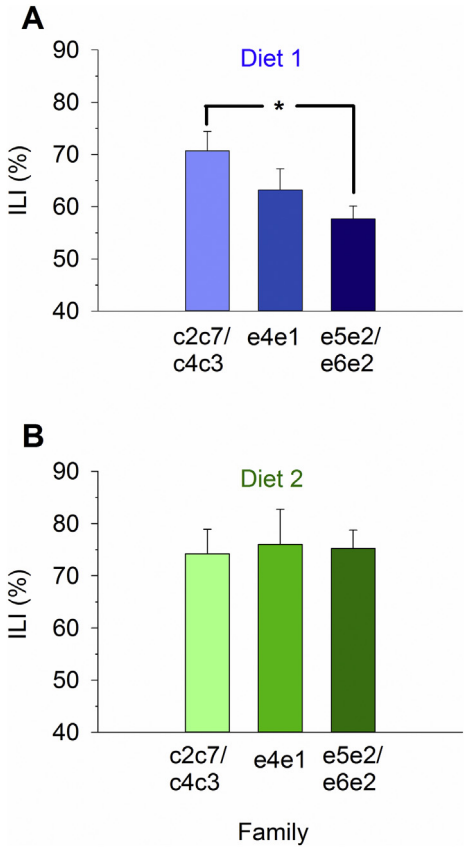

Fig. 7. Effects of diet (A: D1; B: D2) on intestinal length index (ILI). Families are grouped according to their genetic background and growth performance. Values are the mean ± sem of 8 fish per family. Tukey post hoc test, $^{*}P < 0.05$.

composition and function.

As in other fish, both liver and adipose tissue are important energy reservoirs in gilthead sea bream, and the resulting HSI and MSI were affected herein by both diet and genotype. As a general rule, D2 fish exhibited higher HSI and lower MSI than fish feed the control diet. The increase of HSI in fish fed plant-based diets is a common feature in gilthead sea bream (Cruz-Garcia et al., 2011; Benedito-Palos et al., 2016; De Francesco et al., 2007) and other farmed fish (Cabral et al., 2013; Riche and Williams, 2011) as the result, at least in part, of an increased trafficking of lipids from adipose tissue towards the liver (Benedito-Palos et al., 2010; Cruz-Garcia et al., 2011). It is noteworthy that body fat re-allocation reflects a wide-range of nutritional dysfunctions. For instance, HSI is lowered by deficiencies in minerals and vitamins, whereas hepatomegaly with signs of steatosis mostly reflects deficiencies in essential fatty acids, especially exacerbated by overwintering (Ballester-Lozano et al., 2015). Likewise, MSI is increased by phosphorous deficiencies, whereas the opposite occurs with deficiencies in sulfur amino acids, essential fatty acids, phospholipids and vitamins. However, the diets used herein were formulated to avoid all those deficiencies, thus variations in HSI and MSI between diets and among families may result from different adaptive mechanisms to cope with plant-based diets and fast growth. Moreover, as we observed in the present study, experimental evidence indicates that HSI is regulated genetically in farmed fish (Dekić et al., 2016; Crouse et al., 2018). Likewise, we previously reported that the concurrence of high feed intake and low MSI, in combination with a slight increase of HSI without signs of pathological damage, are especially valuable features in a fast growing strain of gilthead sea bream (Simó-Mirabet et al., 2018b). This agrees with the current view that fish with genetically low body lipid content grow more efficiently (Kause et al., 2016). The ultimate mechanisms remain poorly studied, and different sensors of energy and lipid metabolism (e.g., *sirts*, *ppara*, *pparγ*, *elov5*) constitute a suited toolbox to assist future studies on genotype by nutrient interactions, as they exhibit strong family effects in both gilthead sea bream (Simó-Mirabet et al., 2018b) and salmon (Morais et al., 2011, 2012).

In summary, selected fish from the PROGENSA broodstock grew efficiently with both a standard and a well-balanced plant-based diet with a high replacement of FM and FO. However, selection for growth has a major effect on growth trajectories through the production cycle, favoring a more continuous rather than a catch-up growth. There is also a significant effect of the genotype on tissue biometrics, with fast growing families exhibiting lower HSI and/or MSI in combination with the capacity to enlarge their intestines when consumed enriched plant-based diets. Further studies are in progress for the better characterization of selected families by biochemical, histological, transcriptomic and metagenomics analyses, in combination with behavior and diseases challenges. These ongoing studies will broaden our understanding of the effects of growth selection on other gilthead sea bream traits with relevance for production under fish farm conditions.

Author contributions

JP-S coordinated and designed the study; CB and JMA designed and conducted the broodstock crosses; VK formulated the experimental diets; VEA, HSS and JM-A genotyped all fish and conducted parents assignments; EA and MA raised larvae fish; EP, PS-M, ER-M, FN-C, VH, JM-S and JC-G grow out fish from early life stages to the end of trial; EP, PS-M and JP-S analyzed all data on fish performance; EP and JP-S wrote the manuscript; all authors read, edited and approved the final manuscript.

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Declarations of interest

None.

Statement of relevance

Genetic selection for faster growth does not compromise the use of alternative plant-based diets in gilthead sea bream.

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