Aquaculture Reports 30 (2023) 101582

Contents lists available at ScienceDirect

Aquaculture Reports

journal homepage: www.elsevier.com/locate/aqrep

Genetic parameters and genomic prediction of resistance to koi herpesvirus disease using a low-density SNP panel on two Amur mirror carp populations

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ARTICLE INFO

Keywords:
Heritability
Breeding program
Common carp
Selection
Breeding value

ABSTRACT

Koi herpesvirus disease (KHVD), caused by Cyprinid herpesvirus-3 (CyHV-3), is one of the most serious threats to carp farming. In the present study, we investigated the efficiency of a low-density (LD) SNP panel for estimating genetic parameters and breeding values to KHVD resistance in the Amur mirror carp (AMC). Two populations (Pop 1 and Pop 2) of AMC generated from unrelated parents were created using a partial factorial design. One-year old fish (Pop 1 = 1500 individuals.; Pop 2 = 1200 individuals) were challenged with CyHV-3 and phenotyped to KHVD resistance. 218 SNPs originating from a medium genotyping platform previously applied to Pop 1 (15615 SNPs; denoted as MD panel) with the highest association to KHVD resistance were used as a LD panel to genotype individuals of Pop 2. Genetic parameters and estimated pedigree-based BLUP (EBV) and genomic-based GBLUP (GEBV_MD and GEBV_LD) breeding values were calculated and obtained for Pop 1 using either pedigree, MD or LD panel and for Pop 2 using either pedigree or the LD panel. The heritability estimates of KHVD resistance were very high for both populations ranging from 0.42 to 0.96. Selection for KHVD resistance in Pop 2 using the LD panel would have led to a relative increase of ~7% in prediction accuracy compared to the pedigree-based selection. Pearson correlation coefficients between pedigree-based and genomic-based estimated breeding values (EBV vs. GEBV_MD; EBV vs. GEBV_LD; GEBV_MD vs. GEBV_LD) showed a strong association for both populations (0.79 – 0.91). In addition, the concordance rate of individuals selected by pedigree-based (EBV) and genomic-based breeding values (GEBV_MD and GEBV_LD) within selection pressures of 5%, 10% and 20% were not statistically different in most cases. In conclusion, the low-density SNP panel could be useful for a selection program focused on the genetic improvement of KHVD resistance.

1. Introduction

Aquaculture is a relatively young industry compared to that of terrestrial animals. Notably, aquaculture has been the fastest-growing food industry worldwide for several decades. This trend is expected to continue in the following years, together with the increasing food demand due to the ever-growing world human population (FAO, 2020). Although technological advances and innovations to improve aquaculture production are on a high level, viral and bacterial infection diseases are still a significant threat to the whole aquaculture sector (Gjedrem, 2005).

Central European aquaculture has been focusing on pond culture with common carp (*Cyprinus carpio* and *Cyprinus rubrofuscus*) as a major fish-species. Nevertheless, summer hypoxia, predation pressures, and disease outbreaks are major threats to carp production (Horváth et al., 2008). Currently, one of the most serious disease is the koi herpesvirus disease (KHVD) which is caused by Cyprinid herpesvirus-3 (CyHV-3), a double-stranded DNA (dsDNA) virus (Aoki et al., 2007; Haenen et al., 2004; Rakus et al., 2013). KHVD is also listed as a notifiable disease by the European Union (Taylor et al., 2010) and the World Organization for Animal Health (OIE, 2018). Although morbidity (the ratio of the sick individuals to the entire population) may reach up to 100%, mortality of common carp stocks exposed to KHV is significantly variable ranging between 5% and 90% (Haenen et al., 2004; Piačková et al., 2013;

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https://doi.org/10.1016/j.aqrep.2023.101582
Received 20 December 2022; Received in revised form 21 April 2023; Accepted 28 April 2023
Available online 5 May 2023

Adamek et al., 2019; Machat et al., 2022).

Generally, common carp strains/hybrids derived from Amur wild carp, were found to be more resistant to KHVD compared to the others (Piačková et al., 2013; Adamek et al., 2019; Nedoluzhko et al., 2020). Also, selective breeding programs have been increasingly focusing on genetic improvement of disease resistance in many aquaculture species with an expected genetic gain of up to 12.5% per generation (Gjedrem and Robinson, 2014). Notably, high heritability estimates for KHVD resistance (0.50 – 0.79) have been previously reported in various carp populations (Ødegård et al., 2010; Tadmor-Levi et al., 2017; Palaiokostas et al., 2018b; Zhao et al., 2020). Furthermore, five significant quantitative trait loci (QTLs), explaining up to 10% of KHVD resistance, have been recently identified by a genome-wide association study (GWAS) in mirror carp strains (Palaiokostas et al., 2018b; Jia et al., 2020). Therefore, a solid genetic potential for the production of genetically improved carp strains with a high level of resistance exists.

Genomic technologies have transformed the field of aquaculture selective breeding, substantially improving the prediction accuracy (Houston et al., 2020). The OTLs can be applied in form of marker-assisted selection (MAS) when genes with relatively large effects on a trait are present. It was the case of the QTL for resistance to infectious pancreatic necrosis (IPN) in Atlantic salmon (*Salmo salar*) (Houston et al., 2008; Moen et al., 2009; Yáñez et al., 2014). Moreover, incorporation of MAS into breeding programs requires also previous knowledge of the genetic architecture of the target trait(s) (Robinson et al., 2022; Song et al., 2022) and the level of linkage disequilibrium between markers and the underlying QTL plays a key role (Goddard, 2005). Unfortunately, most performance traits are polygenic and controlled by many genes with minor effects. In this case, genomic selection (GS) is the preferred approach (Yáñez et al., 2014; Robinson et al., 2022; Song et al., 2022).

Compared to the traditional pedigree-based selection, the genomic selection takes advantage of markers spread across the genome to estimate genetic relationships at a higher resolution (Meuwissen et al., 2001). Therefore, estimates of genomic breeding values (GEBVs) of performance traits using GBLUP (genomic best linear unbiased prediction) models may enable a faster genetic gain than conventional pedigree methods in aquaculture species (Houston et al., 2020; Boudry et al., 2021; Song et al., 2022; Yáñez et al., 2022). Overall, usage of genomic selection in polygenic traits outperformed the pedigree-based or MAS selection, especially in traits that cannot be phenotyped directly on the breeding candidates (e.g. meat quality, slaughter yields and disease resistance) (Sonesson and Meuwissen, 2009; Yáñez et al., 2014; Gjedrem and Rye, 2018 ; Houston et al., 2020; Song et al., 2022).

Even though high-throughput genotyping technologies are becoming more economically affordable, genotyping costs still remain high. Thus, it is important to develop cost-effective genotyping strategies for aquaculture species (Houston et al., 2020; Song et al., 2022; Yáñez, 2022). Several recent studies (Yoshida et al., 2018a; Vallejo et al., 2018; Kriaridou et al., 2020; Tsairidou et al., 2020; Al-Tobasei et al., 2021; Griot et al., 2021; Song and Hu, 2022) focusing on optimizing GS have shown that using low-density SNP panels (1000 – 6000 SNPs) may give almost identical prediction accuracy compared to medium/high-density ones. In addition, 200 – 3000 SNPs still gave better selection accuracies than pedigree-based approaches. Hence, finding the optimal balance between economic cost associated with the density of a SNP panel and prediction accuracy could facilitate the implementation of breeding programs exploiting genomics in some fish species.

This study aimed to assess the genetic parameters and the prediction accuracy for KHVD resistance on two Amur mirror carp populations using either a low-density or a medium-density SNP panels. Both SNP panels were taken from previous genomic studies on KHVD resistance in Amur mirror carp (Palaiokostas et al., 2018b; Palaiokostas et al., 2019).

2. Material and methods

2.1. Ethics statement

The present study was performed in accordance with the law on the protection of animals against cruelty (Act No. 246/1992 Coll. Of the Czech Republic) and was approved by the expert committee of the Institutional Animal Care and Use Committee (IACUC). All people conducting the phenotypic recordings (body weight and experimental challenges) were qualified to conduct and manage such kind of experiments on live animals.

2.2. Population origins and disease challenge

The origin of the Amur mirror carp (AMC) populations used in this study and the details of the KHVD challenge experiments have been fully described previously (Pop 1: Palaiokostas et al., 2018b; Pop 2: Prchal et al., 2021). In brief, the study was performed on two populations of Amur mirror carp that were established at the University of South Bohemia in České Budějovice, Czech Republic in May 2014 (Pop 1) and 2017 (Pop 2) using an artificial fertilization (Vandeputte et al., 2004). Pop 1 was set from 20 dams and 40 sires (four factorial crosses of five dams x ten sires), Pop 2 was set from 27 dams and 29 sires (three factorial crosses of eight dams and seven sires and one factorial cross of eight dams and six sires). After first the growing season in temperate climate, 1500 individuals out of Pop 1 and 1200 individuals out of Pop 2 were randomly chosen, PIT-tagged, fin-clipped, weighed for body weight (BW) to nearest 0.1 g and measured for standard length (SL) to nearest mm. BW and SL records were then used to calculate Fulton's condition coefficient as $FC = 10^5 * (BW / SL^3)$.

The KHVD experimental challenges were performed in both populations using the same protocol. The challenged fish were first acclimatized together with Koi carp, serving as a control, for five days at water temperature of 22 °C and bathed in FMC solution (formalin, malachite green, methylene blue using a dose of 2 mL per 100 L of water) to eliminate ectoparasites. A week later, the fish were transferred to the Veterinary Research Institute (VRI) in Brno to perform the KHVD experimental challenge test. The experimental challenge was performed by cohabitation in a tank of 1.4 m^3 with recirculation and biological filtration. A small sample ($n = 20$) of Koi carps received an intraperitoneal injection with KHV culture established according to standardized protocol by Piačková et al. (2013). Those animals cohabitated alongside the AMC populations and the rest of Koi carps (~ 200 fish). Mortality of individual fish was recorded twice a day for a period of 35 days post infection (dpi) in Pop 1 and 41 dpi in Pop 2 (until no mortality or disease symptoms appeared). After that period, mortalities were negligible. Resistance to KHV was recorded as a binary trait (0 for dead fish and 1 for alive fish). Presence of KHV in a sample of dead fish ($n = 100$) was confirmed by PCR according to guidelines by the Centre for Environment, Fisheries and Aquaculture Science, United Kingdom (Cefas) (Pokorova et al., 2010). In total, phenotypic records regarding growth-related traits and survival/mortality from experimental challenges were documented for 1425 (Pop 1) and 1135 (Pop 2) individuals.

2.3. Genotypes and parentage assignment

Restriction-site associated DNA sequencing (RAD-seq) was applied to generate a medium-density (MD) genotypic panel including 15615 SNPs. Details on the MD SNP panel were reported by Palaiokostas et al. (2018a) and Palaiokostas et al. (2019). A low-density (LD) 218 SNP subset (Supplementary Table S1) derived from the MD panel with the highest association to KHVD resistance (based on their *p*-values) and spread across the carp genome was also generated.

Genotyping of Pop 2 and their parents was performed by LABOGENA-DNA, the French laboratory for DNA extraction and genotyping (ISO 170025 accredited, Jouy-en-Josas, France). From the initial

LD SNP subset (218), only SNPs with a call rate higher than 0.97, no significant deviation from Hardy- Weinberg equilibrium (p-value > 0.0001), and a minor allele frequency (MAF) higher than 0.05 were retained for further analysis. In addition, samples in which less than 90% of SNPs were genotyped were removed. In total, 183 (Pop 1) and 165 (Pop 2) SNPs of the LD SNP panel passed quality-control filtering.

Parentage assignment for both populations was performed using the R package hsphase version 2.0.2 (Ferdosi et al., 2014) and validated also using APIS package (Griot et al., 2020) with a maximum allowed genotyping error set to 2%.

2.4. Estimation of genetic parameters

Heritabilities for KHVD resistance (overall binary survival; 0 = dead, 1 = alive) were calculated using either a pedigree-based relationship matrix or a genomic relationship matrix using LD SNPs subset for both studied populations (Pop 1 and Pop 2). Pedigree-based and MD SNP panel-based heritability estimates were available for Pop 1 from a study by Palaiokostas et al. (2018b) and presented here for comparison.

Variance components of KHVD resistance were estimated using either a linear model using AIREMLF90 (Misztal et al., 2002) or a threshold model using THRGIBBSF90 (Tsurata and Misztal, 2006). The following animal models, excluding (1) and including the maternal effect (2) to specifically test effect of the model on heritability estimates, were applied:

$$\boldsymbol{y}=\boldsymbol{Xb}+\boldsymbol{Zu}+\boldsymbol{e}, \quad (1)$$

$$\boldsymbol{y}=\boldsymbol{Xb}+\boldsymbol{Zu}+\mathbf{T}\boldsymbol{m}+\boldsymbol{e}, \quad (2)$$

where $\boldsymbol{y}$ is the vector of the observations of KHVD resistance, $\boldsymbol{X}$ and $\boldsymbol{Z}$ are the corresponding design matrices for the intercept and the additive genetic effects of the animal, $\boldsymbol{b}$ is the vector of the intercept for KHVD resistance, $\boldsymbol{u}$ is the vector of random animal effects $\sim N(0, \mathbf{A}\sigma^2_g)$ with $\mathbf{A}$ corresponding to the pedigree-based relationship matrix or the genomic relationship matrix $\mathbf{G}$ (Van Raden, 2008) based on LD markers (Pop 1 – 183 SNPs, Pop 2 – 165 SNPs) and σ^2_g is the additive genetic variance. $\mathbf{T}$ corresponds to the incidence matrix relating KHVD resistance with maternal effects $m \sim N(0, \mathbf{I}\sigma^2_{me})$, $\mathbf{I}$ is the identity matrix, $\mathbf{m}$ is the vector of random maternal effect and σ_{me} is the corresponding maternal variance. Lastly, $\boldsymbol{e}$ is the vector of residuals $\sim N(0, \mathbf{I}\sigma^2_e)$ and σ^2_e the residual variance.

Heritability for KHVD resistance was estimated using the following formula (both populations):

$$h^2=\sigma^2_g/(\sigma^2_g+\sigma^2_e)$$

while in the case of model (2), heritability for KHVD resistance including maternal effect was calculated as (only Pop 2):

$$h^2=\sigma^2_g/(\sigma^2_g+\sigma^2_{me}+\sigma^2_e)$$

while the random maternal effect was calculated as follows (only Pop 2):

$$m^2=\sigma^2_{me}/\sigma^2_g+\sigma^2_{me}+\sigma^2_e$$

With the linear model, the observed values for heritability of KHVD resistance were subsequently transformed to the underlying normally distributed liability scale using the formula by Dempster and Lerner (1950). In the case of the threshold model, the variance components were estimated using a Gibbs sampler with 100,000 iterations, 10,000 of burn-in and keeping one sample every 100 iterations for posterior analysis. Convergence of the resulting posterior distributions was assessed visually after running POSTGIBSSF90 (inspecting the resulting MCMC plots). Heritability estimates using the linear model were considered significant when the difference of additive genetic effect in –2 log-likelihood was higher than the threshold value for $p < 0.05$ of a $\chi 2$ distribution with 1 degree of freedom (Pinheiro and Bates, 2000). The significance of heritability estimates using threshold was evaluated based on the 95% highest posterior density interval and the standard error (SE) was calculated as SE = (upper limit – lower limit) / 3.92 (Mohr et al., 2021).

2.5. Association analysis

To test the association between the selected subset of LD SNP panels and resistance to KHV on Pop 2, a classical association analysis was performed using R/gaston (Perdry and Dandine-Roulland, 2016).

The mixed model applied for KHVD resistance was as follows:

$$\boldsymbol{y}=\boldsymbol{Xb}+\boldsymbol{Zu}+\boldsymbol{e},$$

with the same notation as described in model (1) with the addition of including each SNP as a fixed effect. The -log10 of the p-values were compared to the genome-wide significance threshold ($\alpha = 0.05$) after Bonferroni correction (0.05 / N), where N represents the number of QC-filtered SNPs.

2.6. Estimation of breeding values

Both pedigree-based (PBLUP) breeding value estimates (EBVs) and genomic-based (GBLUP) breeding value estimates using MD (GEBV_MD) and LD (GEBV_LD) SNP panels were calculated using the software package BLUPf90 (Misztal et al., 2014). The general form of the fitted model was as in model (1). Thus, for Pop 1 we had available EBVs, GEBV_MD and GEBV_LD, for Pop 2 we had available only EBVs and GEBV_LD.

The Pearson correlation coefficient was used to evaluate the linear correlation of the breeding values as follows: EBV vs. GEBV_MD (Pop 1), GEBV_MD vs. GEBV_LD (Pop 1) and EBV vs. GEBV_LD (Pop 1 and Pop 2). In addition, the concordance rate of individuals ranked as the best according to above mentioned models of breeding value estimates was assessed for scenarios of 5%, 10% and 20% of selection pressure.

To evaluate the prediction accuracy of (G)EBVs on Pop 2, 50 replicates of Monte Carlo 'leave-one-group out' cross-validation tests were run considering the same procedure as described in D'Ambrosio et al. (2020). For each replicate, approximately 20% of the fish were randomly chosen as a validation set, while the rest were used as a training set. The prediction accuracy (r) for each replicate was computed as:

$$r=cor((\mathbf{G})\mathbf{EBV},\mathbf{y})/\mathrm{h},$$

where cor ((**G**)**EBV**, **y**) is the correlation between the (G)EBV and the phenotypes of the individuals belonging to the validation population, and h is the square root of the genomic heritability estimated with a linear model. The prediction accuracies and the inflation coefficients of the tested models (PBLUP, GBLUP) were presented as average values over all 50 replicates. In the absence of selection bias, the inflation coefficient is expected to be equal to 1; in the case of EBV overdispersion (inflation), the coefficient is below 1, and in the case of EBV underdispersion the value is above 1.

3. Results

3.1. Growth-related traits and disease challenge

The mean body weight of the challenged fish was 16.3 ± 4.6 g (Pop 1) and 25.7 ± 8.3 g (Pop 2), while the mean Fulton's condition coefficient was 3.5 ± 0.3 (Pop 1) and 3.1 ± 0.2 (Pop 2).

On Pop 1, mortality began at 12 dpi, reaching a maximum daily rate between 21 and 24 dpi (98 – 130 dead individuals per day), decreasing thereafter until the end of the challenge at 35 dpi without mortality (Palaiokostas et al., 2018b). On Pop 2, mortalities began also at 12 dpi, reaching a maximum daily rate between 17 and 18 dpi (98 – 106 mortalities per day), while the challenge test ended at 41 dpi (See

Supplementary Fig. S1). Infected and dying fish were displaying typical KHVD clinical and pathological patterns. (e.g., weakness, lethargy, loss of equilibrium and disorientation, erratic swimming, sunken eyes, excessive mucous production, pale discoloration of the skin and gills or reddened skin, hemorrhagic lesions on the skin and gills, and fin erosion). All fish samples screened for KHV presence (in both experimental challenges) by nested PCR were positive. Overall, total mortality reached 66% for Pop 1% and 56% for Pop 2.

3.2. Parentage assignment

In Pop 1, 1259 offspring out of 1425 were uniquely assigned to a parental pair (88.3%), comprising 195 full-sib families from 20 dams and 40 sires. The number of progeny per sire varied from 7 to 53 (the average was 30). The number of progeny per dam varied from 9 to 99 (the average was 61). In Pop 2, 758 individuals out of 1135 were uniquely assigned to a parental pair (66.8%) using 165 SNPs, comprising 216 full-sib families from 27 dams and 29 sires. The number of progeny per sire varied from 11 to 46 (the average was 29). The number of progeny per dam varied from 4 to 49 (the average was 27).

3.3. Genetic parameters

Heritability estimates for KHVD resistance using a linear and a threshold model are listed in Table 1. The pedigree heritability of KHVD resistance on Pop 1 was 0.61 ± 0.07 (Palaiokostas et al., 2018b). The genomic heritability was 0.50 ± 0.06 using MD SNP panel (Palaiokostas et al., 2018b), while using LD SNP panel heritability decreased to 0.36 ± 0.04. Random maternal effect was found to be negligible and was excluded from the model in Pop 1. In Pop 2, heritability estimates were 0.96 ± 0.09 (pedigree) and 0.68 ± 0.09 (LD SNP panel). Heritability estimates using the model (2) with the random maternal effect were slightly different (0.78 ± 0.25 for pedigree and 0.45 ± 0.16 for LD SNP panel). Similar values were found using a threshold model without maternal effect (0.93 ± 0.07 for pedigree and 0.66 ± 0.07 for LD SNP panel), while with maternal effect the heritability were 0.85 ± 0.14 for pedigree and 0.42 ± 0.10 for LD SNP panel.

3.4. Association analysis

Association analysis identified only one SNP surpassing the genome-wide significant threshold (Fig. 1), indicating possible loss of linkage disequilibrium between the QTL and the markers that most likely existed only within families of Pop 1. The logarithmic quantile-quantile (QQ) plot for the association analysis did not show any abnormal deviation (Fig. 2).

Table 1
Heritability estimates (± standard error) ± of KHVD resistance estimated with threshold or linear model using either the pedigree-based (P) or the genomic relationship matrix (G) in both studied populations (Pop 1 and Pop 2).

KHVD Resistance	Model	h^2	h^2 (maternal effect) **
Pop 1 – P *	Threshold	0.61 ± 0.07	-
Pop 1 – G (MD)*	Threshold	0.50 ± 0.06	-
Pop 1 – G (LD)	Threshold	0.36 ± 0.04	-
Pop 2 – P	Linear	0.96 ± 0.09	0.78 ± 0.25
Pop 2 – G (LD)	Linear	0.68 ± 0.09	0.45 ± 0.16
Pop 2 – P	Threshold	0.93 ± 0.07	0.85 ± 0.14
Pop 2 – G (LD)	Threshold	0.66 ± 0.07	0.42 ± 0.10

MD: Medium-density SNP panel (15615 SNPs)
LD: Low-density SNP panel (183 SNPs – Pop 1, 165 SNPs – Pop 2)
* taken from Palaiokostas et al. (2018b)
* * model including random maternal effect

3.5. Estimated breeding values

Pearson correlations coefficients between the estimated breeding values of KHVD resistance (Fig. 3) were very high for EBV vs. GEBV_MD and GEBV_MD vs. GEBV_LD (0.91 and 0.86 respectively) in Pop 1. Furthermore, correlations between EBVs and GEBV_LD were still high and consistent for both investigated populations (0.81 in Pop 1 and 0.79 in Pop 2).

The extent of selecting the same individuals (from Pop 1 and Pop 2) using different models for breeding value estimation under three selection pressure scenarios (5%, 10% and 20%) is shown in Table 2. Concerning the models of breeding value estimation within Pop 1 and Pop2, the lowest concordance rate of breeding candidates was seen in the case of EBV vs. GEBV_LD (~ 32%) in Pop 2. Moreover, the values for Pop 2 were generally lower than for Pop 1. Concerning the concordance rates between populations for EBV vs. GEBV_LD, the highest difference was observed for a selection pressure of 20% (72.5% and 62.3% common candidates, respectively), which was the only significant difference among tested selection pressures. In general, the overall number of common candidates (Pop 1) meeting the selection criteria for GEBV_MD vs. GEBV_LD was lower than for EBV vs. GEBV_MD. However, differences in concordance rates of pairs of different breeding value estimate models (EBV vs. GEBV_MD, EBV vs. GEBV_LD and GEBV_MD vs. GEBV_LD) were not statistically significant within the tested selection pressure values.

In terms of prediction accuracy, GBLUP had on average 7% higher accuracy (0.66 ± 0.06) than PBLUP (0.62 ± 0.07) in Pop 2 (Fig. 4). A pairwise t-test showed that the difference in prediction accuracy between PBLUP and GBLUP models was significant ($p = 0.006$). Finally, the inflation coefficients were not statistically different from 1 and were slightly lower for GBLUP (0.88 ± 0.09) than for PBLUP (0.99 ± 0.12).

4. Discussion

Our study focused on evaluating the implementation potential of a low-density (LD) SNP panel for predicting KHVD resistance in common carp based on the animal's genomic profile. Two populations of Amur mirror carp (AMC) challenged to KHVD resistance were used. As already mentioned, the LD SNP panel was derived from data from our previous study (Palaiokostas et al., 2019). Thus, we compared genetic parameters estimates and prediction accuracies of breeding value estimates using different approaches with our previous results on Pop 1 (Palaiokostas et al., 2018b; Palaiokostas et al., 2019).

There was substantial variation in survival of fish challenged to KHVD among half-sib families of sires (Pop 1: 9 – 81%; Pop 2: 0 – 93%) and dams Pop 1: 0 – 53%; Pop 2: 0 – 96%) in both populations (data not shown). Such variation may suggest the existence of considerable genetic variation for KHVD resistance. Indeed, heritability estimates for resistance to KHVD were high in Pop 1 (Palaiokostas et al., 2018b) using both pedigree and genomic relationship matrix (0.50 ± 0.06) with the MD SNP markers. Using the LD SNP panel, we observed ~30% reduction (from 0.50 to 0.36) in the estimated heritability of KHVD. Similarly, Kriaridou et al. (2020) showed a reduction of heritability estimates (~50%) in various traits across different fish species using 200 SNPs compared to the full-density panels. Therefore, low-density SNP panels cannot fully capture the additive genetic variance, and their performance could be highly dependent on SNP selection. In the current study, a subset of SNPs was primarily selected based on their prior association with KHVD resistance on Pop 1. In Pop 2, the heritability estimates calculated with linear model or threshold model were even higher (0.96 ± 0.09 and 0.93 ± 0.07 using the pedigree, respectively; 0.68 ± 0.09 and 0.66 ± 0.07 using the LD SNP panel, respectively). It appears, that at least in the case of the pedigree model, the heritability estimate was inflated. The parentage assignment rate in Pop 2 using the LD SNP panel was worse (66.8%) than the full-density panel in Pop 1 (88.3%). The reason for that may be due to the fact that the LD SNP panel set-up

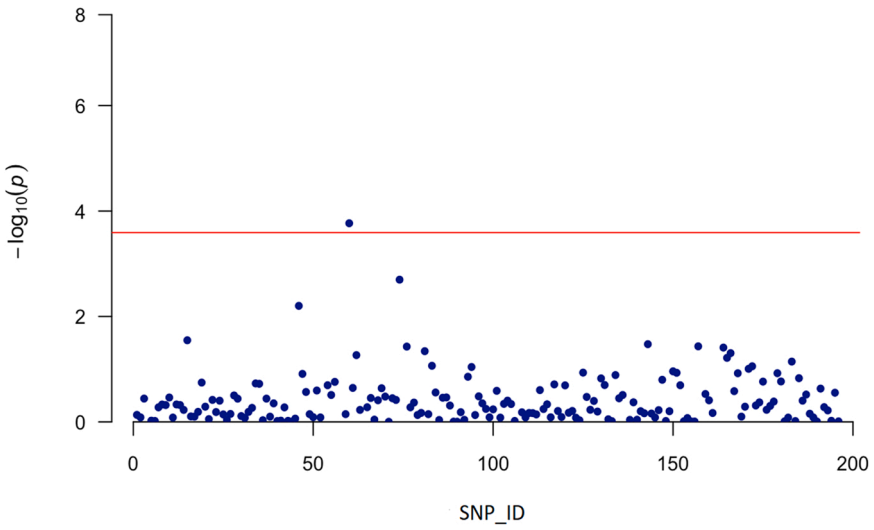

Fig. 1. Association plot using LD SNP markers for KHVD resistance on Pop 2. The red horizontal line corresponds to the genome-wide significance threshold at 5%.

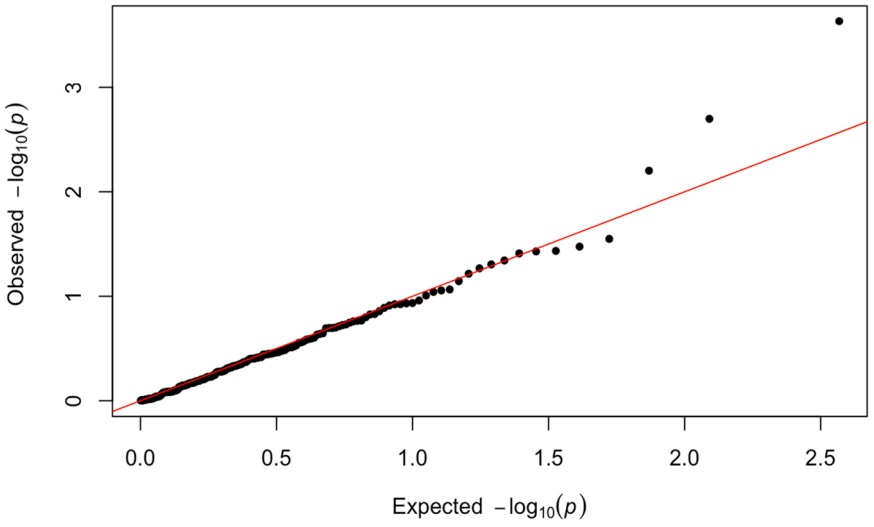

Fig. 2. Logarithmic quantile-quantile (QQ) plot for the association analysis obtained p-values.

prioritized SNPs associated with KHVD resistance over the ability to discriminate between closely related parents. As such, the heritability estimates from Pop 2 were calculated with ~40% less individuals than the ones in Pop 1.

Moreover, the random maternal effect might partially explain the high pedigree-based heritability in Pop 2. When a model including the maternal effect was used, a significant reduction of heritability estimates was observed on both the linear (0.78 ± 0.25 – P; 0.45 ± 0.16 – G) and threshold model (0.85 ± 0.14 – P; 0.42 ± 0.10 – G) (Table 1). Notably, studies concerning maternal effects on disease resistance in aquaculture species are rare. However, an underlying epigenetic factor was suggested to be a causative factor for the observed maternal effect related to cold tolerance in blue tilapia (*Oreochromis aureus*) (Nitzan et al., 2016) and hypoxia tolerance in rainbow trout (*Oncorhynchus mykiss*) (Prchal et al., 2018). Overall, regardless of the studied population or model used for variance components estimation, the resistance to KHVD is a highly heritable trait. These findings are in accordance with the results of previous studies that also highlighted substantial genetic variation of host resistance to KHVD (Ødegård et al., 2010; Tadmor-Levi et al., 2017).

In our previous study on Pop 1 (Palaiokostas et al., 2018b), a QTL associated with KHVD resistance was detected on chromosome 33. However, this QTL accounted for only 7% of the genetic variance related to KHVD resistance, highlighting that multiple additional genomic regions could be involved. Moreover, an association analysis performed on Pop 2 revealed only one significant SNP surpassing the genome-wide significant threshold related to KHVD resistance. Our findings suggest a possible loss of linkage equilibrium between the QTL and the markers that most likely existed only within families of Pop 1 and not across families/populations of the whole AMC stock due to the recombination events. Therefore, the linkage phase between the marker and the QTL should be determined in each generation and separately for each family/population (Wientjes et al., 2013). Thus, genomic selection for KHVD resistance seems to be the most appropriate approach. Yet, the genotyping costs are still relatively high, and the reference population size and SNP marker density create the two major cost drivers (Rajsic et al., 2016; Kriaridou et al., 2020; Griot et al., 2021). Therefore, assessing the efficiency of cheaper low-density SNP panels for estimating breeding values of KHVD resistance has been the main intent of the present study. Our results show that despite lower heritability estimates in Pop 2, usage of LD panel of 165 SNPs would increase of ~ 7% the prediction accuracy (0.65) of breeding values compared to a pedigree-based calculations (0.62) considering a reference population of ~ 600 individuals. In our previous study on Pop 1 (Palaiokostas et al.,

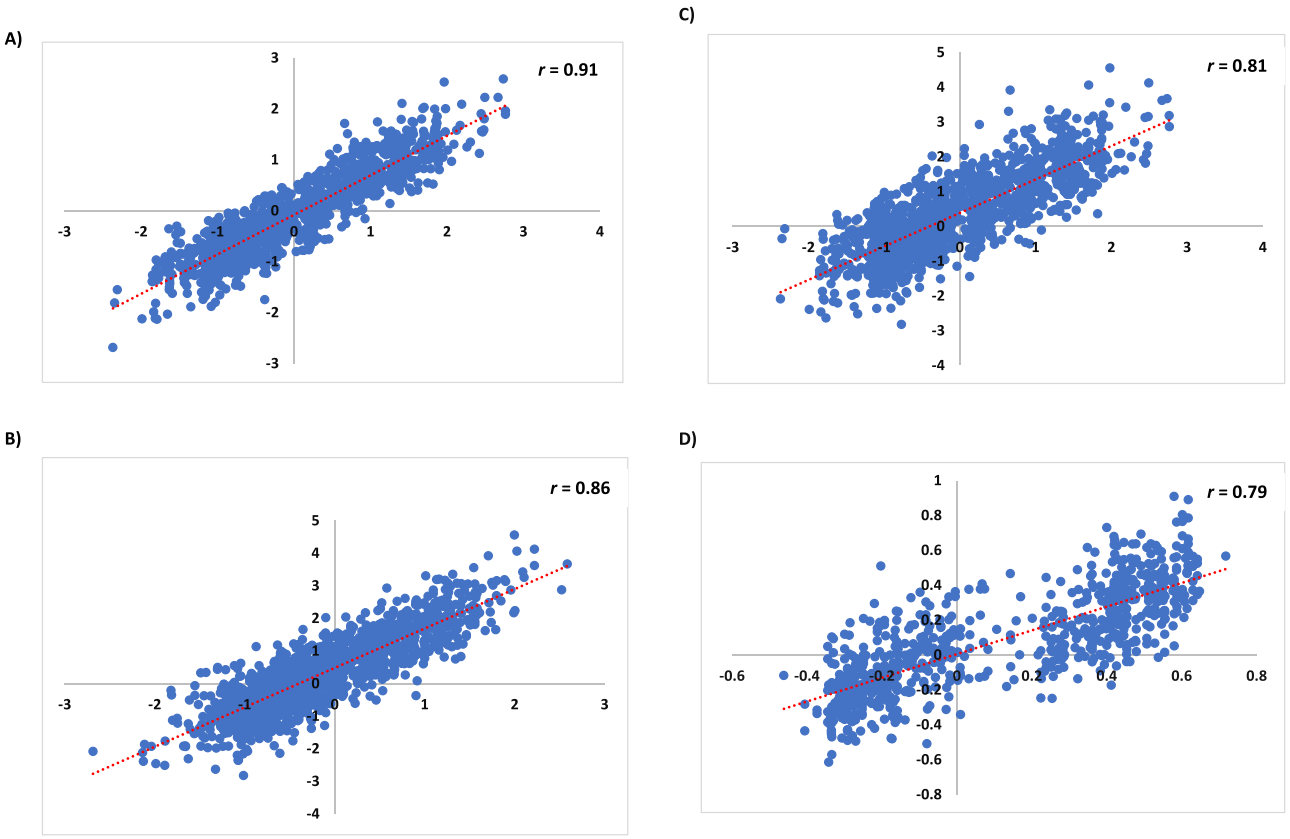

Fig. 3. Correlations between estimated breeding values: EBV vs. GEBV_MD (A), GEBV_MD vs. GEBV_LD (B) and EBV vs. GEBV_LD (Pop 1 = C, Pop 2 = D).

Table 2
Ratio of common individuals (%) in Pop 1 and Pop 2 that would pass the selection threshold under selection pressures of 5%, 10% and 20% when comparing different models for estimating breeding values (EBV, GEBV_MD and GEBV_LD).

Population	Selection pressure (%)	EBV vs. GEBV_MD	GEBV_MD vs. GEBV_LD	EBV vs. GEBV_LD
Pop 1	5	48.4*(30/62)*	54.8*(34/62)*	38.7*(24/62)*
Pop 1	10	60.8*(76/125)*	60.0*(75/125)*	49.6*(62/125)*
Pop 1	20	78.1*(196/251)*	75.7*(190/251)*	72.5*(182/251)**
Pop 2	5	x	x	32.4*(12/37)*
Pop 2	10	x	x	44.0*(33/75)*
Pop 2	20	x	x	62.3*(94/151)**

Values indicated with * are mutually significantly different at $\alpha = 0.05$ using the $\chi 2$ test

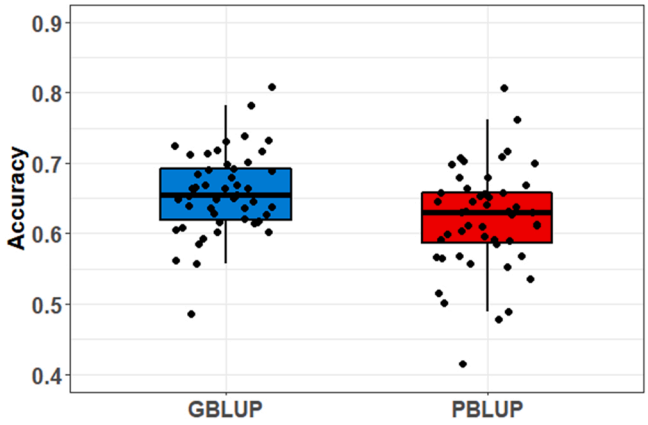

Fig. 4. Prediction accuracy of PBLUP and GBLUP models for KHVD resistance in Pop 2 for each of 50 replicates.

2019), the prediction accuracy using PBLUP was 0.49 while genomic prediction models showed 8% and 18% higher prediction accuracies with dependence on the tested scenarios (kinship of training and validation set, number of SNPs). Several recent studies focused on the optimization of genomic prediction using low-density SNP panels in aquaculture showed that using 200 – 500 SNPs (Vallejo et al., 2018; Al-Tobasei et al., 2021), 1000 – 2000 SNPs (Kriaridou et al., 2020) and ~ 3000 SNPs (Yoshida et al., 2018a; Griot et al., 2021; Song and Hu, 2022) were sufficient for obtaining a relatively high prediction accuracy outperforming the PBLUP.

Overall, the LD SNP panel used in our study is valuable for predicting breeding values of KHVD resistance across Amur mirror carp stocks. Studies performed on Australian sheep (Moghaddar et al., 2019) and dairy cattle (van den Berg et al., 2016; Raymond et al., 2018) showed that the prioritization of LD SNPs by preselected from GWAS could be beneficial. Similarly, Yoshida and Yáñez et al. (2022) found that preselected SNPs from GWAS can improve the accuracies of breeding values prediction for growth under chronic thermal stress in rainbow trout, and the use of high-density SNP panels might be inefficient. Hence, non-random SNP selection can increase the prediction accuracy of low-density SNP panels (Kriaridou et al., 2020).

It is known that the magnitude of genetic relationships between the training and the validation population strongly affects the accuracy of breeding values prediction (Pszczola et al., 2012; Palaiokostas et al., 2019; Griot et al., 2021; Fraslin et al., 2022). Similarly, the effectivity of LD SNP panel for prediction of breeding values strongly correlates with level of the genetic relatedness of training and selection stocks

(Palaiokostas et al., 2019; Kriaridou et al., 2020; Fraslin et al., 2022). In breeding programs focused on disease resistance traits, the reference population generally consists of challenged individuals that are full- or half-sibs of the breeding candidates (Ødegård et al., 2011). Moreover, the ancestral effective population size estimated for AMC breed was found to be low ($n = 33$) by Saura et al. (2021). In addition, high breeding values prediction accuracy using LD SNP panels were observed in traits displaying high heritability estimates (Sonesson and Meuwissen, 2009). Thus, the relatively high breeding value prediction accuracy achieved with a panel of only 165 SNPs in our study might be given the combination of close family relationships between the sampled animals and high heritability estimates of KHVD resistance. Still, both phenotyping and genotyping of the training population for KHVD resistance must be performed every generation to achieve high efficiency in selection of breeding candidates resistant to KHVD using the LD SNP panel in the selection population.

On the other hand, the future reliability of low-density SNP panels in future generations may fluctuate due to possible recombination between the SNP alleles and the underlying QTL(s) controlling the resistance to KHVD. As a result, genotype imputation from very low-density panels of 100 – 200 SNPs (progeny) to medium-density SNPs of 1000 – 5000 SNPs (parents) might be a useful alternative strategy to reduce the overall genotyping costs (Kriaridou et al., 2020). Previous studies have shown a high potential for imputation to achieve prediction accuracy close to the value obtained by medium-density SNP panels (Tsai et al., 2017; Yoshida et al., 2018b; Tsairidou et al., 2020).

The Pearson correlation analysis between pedigree-based and genomic-based (MD and LD) breeding values estimates showed a strong association. More specifically, we observed in Pop 1 a very high correlation between EBVs and GEBVs_MD (0.91) and only a slight decrease between EBVs and GEBV_LD (0.81). Similarly, the relationship between the genomic prediction of GEBV_MD and GEBV_LD was high (0.86), further suggesting that the LD SNP panel might be sufficiently efficient for the accurate prediction of KHVD resistance. Additionally, the correlation between EBVs and GEBV_LD in Pop 2 showed the same linear relationship (0.79). These results are in line with the ones observed in Atlantic salmon (Bangera et al., 2017) for resistance against *Piscirickettsia salmonis* (0.76–0.81). In contrast, only a moderate correlation (~0.60) was found in rainbow trout for bacterial cold water disease resistance (Vallejo et al., 2016) which indicated that EBVs and GEBVs were not similar predictors of genetic merit.

Upon further investigation, the ranking of the animals did not remain consistent between the EBVs and GEBVs using different scenarios. More specifically, we mutually compared the concordance rates of individuals in both Pop 1 and Pop 2 that would pass the selection threshold under different selection pressures (5%, 10% and 20%) based on breeding value estimates derived from different models (pedigree, HD SNP panel and LD SNP panel). We found that i) the overall ratio of common individuals (individuals that would be selected in both methods) grew with lowering the selection pressure, ii) the number of common individuals among any pair of methods used for calculating breeding values within given selection pressure did not differ significantly in Pop 1 and iii) the ratio of common individuals in the case of the EBV vs. GEBV_LD scenario between Pop 1 and Pop 2 within the given selection pressure differed significantly only for a selection pressure of 20%. Nevertheless, it must be stressed that some SNPs might not be informative in all AMC stocks. Re-rankings of top-selected animals depending on tested scenarios (size of SNP chip, studied population, statistical models etc.) differed up to 45% in dairy cattle (Krejčová et al., 2007; Hanna et al., 2014). Even though the LD panel of 165 SNPs in our study could be sufficiently reliable for a selection program on improving KHVD resistance in AMC, it might be beneficial to construct LD SNP panel with a slightly higher number of informative SNPs.

5. Conclusions

Heritability estimates were substantially high in both populations regardless of the model and approach used (pedigree, LD or MD genomic information). Thus, resistance to KHVD is a prospective trait to be genetically improved by a selection program. Furthermore, implementing of a low-density SNP panel in our study would increase breeding values prediction accuracy by 7% compared to pedigree-based BLUP in Pop 2. Besides, correlations between pedigree-based and genomic-based (MD and LD) EBVs showed a strong association for both populations (0.79 – 0.91). In addition, the concordance rates of top-selected individuals based on breeding values using different selection scenarios were not statistically different in most cases. In conclusion, selected LD SNP panel might be used for relatively accurate prediction of breeding values for KHVD resistance in different stocks of AMC.

CRediT authorship contribution statement

Martin Prchal: Investigation, Conceptualization, Resources, Software, Formal analysis, Writing – original draft. **Christos Palaiokostas:** Investigation, Resources, Software, Writing – review & editing, Methodology, Formal analysis. **David Gela:** Investigations, Resources, Writing – review & editing. **Veronika Piačková:** Investigation, Resources, Writing – review & editing. **Stanislava Reschová:** Investigation, Resources, Writing – review & editing. **Martin Kocour:** Supervision, Conceptualization, Methodology, Investigation, Resources, Software, Formal analysis, Writing – original draft, Project administration; Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgements

This study was supported by the Ministry of Agriculture of the Czech Republic - project of National Agency for Agricultural Research (NAZV) No. QK1910430, Ministry of Education, Youth and Sports of the Czech Republic – project Biodiverzita (CZ.02.1.01/0.0/0.0/16_025/0007370). Part of the data for Pop 1 were obtained due to the support of the European Union's Seventh Framework Programme (FP7 2007-2013) under grant agreement no. 613611 (FISHBOOST).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.aqrep.2023.101582.

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