Aquaculture
Article In Press
Acceptation date : January 2020
https://doi.org/10.1016/j.aquaculture.2020.734986
https://archimer.ifremer.fr/doc/00604/71623/

Genetic relationship between koi herpesvirus disease resistance and production traits inferred from sibling performance in Amur mirror carp

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Abstract :

Koi herpesvirus disease (KHVD) is currently the most serious threat to global carp farming. Prevention is a sensible strategy for tackling this disease and improved genetic resistance of carp strains is a desirable breeding goal. To study the potential for multitrait selection, the objective of the current study was to estimate the genetic correlations between KHVD resistance and production traits in Amur mirror carp. A total of 1500 fingerlings from four factorial crosses of five dams and ten sires were challenged with Koi herpesvirus (KHV). Juvenile growth-related traits were collected on the same individuals before the challenge test. Production traits were measured on siblings of the challenged population at different life stages (yearling to market size). The estimated heritability for resistance to KHVD was 0.43 ± 0.08 on the observed scale and 0.72 ± 0.13 on the underlying liability scale. Most genetic correlations between KHVD resistance and important production traits were insignificant, showing that selection for improved production traits would not increase susceptibility to KHV and vice versa. However, resistance to KHVD was negatively correlated with Fulton's condition factor (FC) after the second overwintering and relative head length (RHL), relative body height (RBH) and relative body width (RBW) from the second growing season to the market size, with a more prolonged body shape of Amur mirror carp (genes from Amur wild

scaly carp, Cyprinus rubrofuscus) being associated with higher KHVD resistance. Intermediate favorable genetic correlations between KHVD resistance and log-log residuals of headless carcass yield (0.37 ± 0.14) and fillet yield (0.44 ± 0.13) at market size suggested that selection for improved yields of edible body parts might indirectly lead to a slight improvement in KHVD resistance and vice versa.

Highlights

► Heritability for Koi herpesvirus disease (KHVD) resistance was high. ► Most genetic correlations between KHVD resistance and important production traits were insignificant. ► KHVD resistance was significantly genetically correlated to body shape traits and slaughter yields.

Keywords : Common carp, KHVD, Body shape traits, Slaughter yields, Heritability, Genetic correlation

1. Introduction

Common carp (*Cyprinus carpio*) is one of the most important cultured fish species globally. However, carp farming faces serious challenges due to disease outbreaks (Haenen et al., 2004; Ødegård et al., 2010; Adamek et al., 2018; Su and Su, 2018; Adamek et al., 2019). Currently, the most serious one is the koi herpesvirus disease (KHVD) that is caused by *Cyprinid herpesvirus-3* (CyHV-3), also called Koi herpesvirus (KHV). KHVD outbreaks have been reported both in European and Asian countries (Haenen et al., 2004; Rakus et al., 2013). The severity of KHVD is pinpointed by its listing as a notifiable disease by the European Union (Taylor et al., 2010) and the World Organization for Animal Health (OIE, 2018). The disease occurs most commonly at water temperatures between 17°C and 26°C (Haenen et al., 2004). Morbidity is often 100 %, but mortality can vary due to different factors and is more likely to occur at higher temperatures (23°C and 28°C) (Hedrick et al., 2000, Yuasa et al., 2008). Therefore, looking to prevent KHVD via selective breeding to produce strains of carp with increased genetic resistance is important for the long-term sustainability of carp aquaculture.

Aquaculture breeding programs are increasingly focusing on genetic improvement of disease resistance (Gjedrem and Robinson, 2014; Yáñez et al., 2014; Gjedrem and Rye, 2018; Robledo et al., 2018). Previous studies have laid the foundation for breeding of KHV-resistant carp strains and have shown that breeding programs could produce carp strains with high level of resistance (Shapira et al., 2005; Piačková et al., 2013; Tadmor-Levi et al., 2017; Palaiokostas et al., 2018). Estimation of genetic correlations between resistance to KHVD and other production traits that may be included in breeding goals, such as growth, body composition and fish welfare traits is of paramount importance. Most evaluations of genetic correlation of disease resistance with other

traits in fish have been focused on growth-related traits, particularly in salmonids (e.g. Yáñez et al., 2016; Flores-Mara et al., 2017; Barría et al., 2019; Gjerde et al., 2019). Prior results demonstrated different genetic relationships between resistance to disease and growth. Therefore, genetic correlations are necessary to be known for each fish species before systematic selective breeding program.

The main aim of this study was to estimate genetic correlations of KHVD resistance with other important production traits in Amur mirror carp from yearlings to market size. Such knowledge will assist in developing a sustainable breeding program for genetic improvement of disease resistance alongside multiple production traits.

2. Materials and methods

2.1. Ethics statement

The entire experiment was performed in accordance with the law on the protection of animals against cruelty (Act No. 246/1992 Col. of the Czech Republic) upon its approval by the expert committee of the Institutional Animal Care and Use Committee (IACUC). All people conducting the trait measurements and challenge test were qualified to conduct and manage such kind of experiments on the live animals.

2.2. Establishment and rearing of experimental stocks

The details of the stocks have been described previously (Palaiokostas et al., 2018 and Prchal et al., 2018ab). In brief, an experimental population of Amur mirror carp was established at the hatchery of Faculty of Fisheries and Protection of Waters of University of South Bohemia in České Budějovice, Vodňany, Czech Republic in May 2014 from artificial spawning according to Vandeputte et al. (2004) using four factorial crosses of five dams and ten sires (20 dams and 40

sires were used in total) allowing up to 200 full-sib families. Randomly sampled progenies from each cross were pooled using approximately equal total volume and stocked into nursery earthen ponds at stocking density of 150,000 larvae / ha. Fish were then reared under semi-intensive pond conditions through the first growing season until October 2014. Following pond harvest a subset of the stock was used for KHVD challenge test (see below). Prior to the test, fish were phenotyped for growth-related traits. In addition, siblings of the challenged stock were grown up to the market size. Stocking density was 6000 ind./ha (mean weight of 336.1 g, coefficient of variation of 19.2%) during the second growing season and 500 ind./ha (mean weight of 1910 g, coefficient of variation of 14.6%) during the last (third) growing season (see box-plots for weight of experimental stocks in S1 figure). The aforementioned 3000 fish were individually tagged using Passive Integrated Transponders (PITs) and then phenotyped for the main production traits after each growing season and each overwintering. At the end of the third growing season, the fish were slaughtered and phenotyped for processing traits.

2.3. KHVD challenge test

A total of 1500 fish were taken at random and PIT-tagged and a sample of fin tissue was taken in autumn 2014 for subsequent DNA analysis (parentage allocation and genomic analysis). These fish were then acclimatized together with Koi carp (n = 215) 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) only for experimental fish to eliminate ectoparasites. Soon after, the fish were transferred to the Veterinary Research Institute (VRI) in Brno in order to perform the KHVD challenge test.

The experimental procedure was the same as described in Palaiokostas et al. (2018). Cohabitation challenge protocol was performed in a tank of 1.4 m^3 with recirculation and biological filtration.

20 fish out of the Koi carp received an intraperitoneal injection with KHV culture established according to standardized protocol by Piačková et al. (2013) and were cohabited with Amur mirror carp and the rest of Koi carps. Mortality of individual fish was recorded twice a day for a period of 35 days post infection (dpi) when mortalities were negligible. Resistance was recorded as 0 for dead fish and 1 for surviving fish. Presence of KHV on samples of dead fish (n = 5) was confirmed in seven time points from 10 to 35 dpi by nested PCR as described by Pokorova et al. (2010).

2.4. Parentage assignment of experimental stocks

Parentage assignment of challenged fish was done on 1500 fish by SNP genotype data (12,311 SNPs grouped in 50 linkage groups) using R software version 3.6.1 (R Core Team, 2019) with hsphase package version 2.0.2 (Ferdosi et al., 2014). Parentage assignment of the second and the third year fish (production traits) was based on the analysis of 12 microsatellite loci and performed using the AccurAssign software, applying a maximum-likelihood method (Boichard et al., 2012). For more details see Palaiokostas et al. (2018) and Prchal et al. (2018b).

2.5. Production traits recording on siblings

Juvenile growth-related traits (body weight – BW and Fulton's condition factor – FC) were measured in the same tagged individuals (n = 1500) from the challenge test. Each individual was weighed (to the nearest 0.01 g) and measured for standard length (SL) (to the nearest 0.1 mm). FC was calculated according to formula: $FC = 10^5 * BW / SL^3$.

After the first overwintering (March 2015), a random sample of 3000 siblings coming from the same stock as the disease challenged animals (being reared in the same pond, i.e. identical

environmental conditions) were phenotyped. Recorded traits included standard length (SL), body length (BL), head length (HL), body height (BH), body width (BWI), and body weight (BW). In addition, biometric indices were calculated as follows: relative body height: RBH = BH/SL, relative head length: RHL = HL/SL and relative body width: RBW = BWI/SL. The survival of those individually tagged fish was recorded before and after the second overwintering period as well as at the end of third growing season (market size). At each of these time points, the following individual traits were recorded: body weight (g), muscle fat by Distell fish fat meter (%), absolute and relative muscle fat change, weight change expressed as specific growth rate (SGR), RBH, RHL, RBW, FC. At the final sampling, the natural logarithm of the weight of each slaughter body part was calculated and regressed on the logarithm of body weight to obtain growth-independent allometry residuals that fix the bias of ratio traits. The log-log residuals of headless carcass yield and fillet yield were recorded as Logr_hl-Carss and Logr_Fill, respectively. Specific details about traits and their calculation are shown in Prchal et al. (2018ab).

2.6. Estimation of genetic parameters

The heritability of KHVD resistance and genetic correlations between KHVD resistance (1214 fish assigned to a parental pair, forming 195 full-sib families) and production traits (1879 fish assigned to a parental pair, forming 199 full-sib families) were estimated using DMU statistical software (Madsen and Jensen, 2013). The following linear animal model was used:

$$\boldsymbol{y} = X\boldsymbol{\beta} + Z\boldsymbol{a} + \boldsymbol{e},$$

where $\boldsymbol{y}$ is the vector of the observations of KHVD resistance and production traits, X and Z are the corresponding design matrices for the fixed effects and the additive genetic effects of the animal, $\boldsymbol{\beta}$ is the vector of the fixed effects for KHVD resistance (with mating design – four

crosses) and production traits (with sex), $\boldsymbol{a}$ is the vector of random animal additive genetic effect that is distributed N(0, $\mathbf{A}\sigma_a^2$), and $\boldsymbol{e}$ is the vector of the random residual effect that is distributed N(0, $\mathbf{I}\sigma_e^2$). **A** is the relationship matrix, **I** is an identity matrix, σ_a^2 is the additive genetic variance and σ_e^2 is the residual variance. Heritability for KHVD resistance was firstly estimated on the observed scale as $h^2 = \sigma_a^2 / \sigma_a^2 + \sigma_e^2$. Subsequently, this value was transformed to the underlying normally distributed liability scale using the formula by Dempster and Lerner (1950). All traits were recorded from the same families and had a common pedigree (family structure), but KHVD resistance and other performance traits were recorded on different individuals. As a result, residual covariance was set to zero between these traits. Estimated genetic correlation was considered significant at $p < 0.05$ when $|r_g| - |1.96 \times S.E.|$ was not zero or less (two-tailed hypothesis) (Coolidge, 2013).

3. Results

3.1. Experimental challenge test

Fish experimentally infected with KHV presented typical clinical and pathological patterns. These symptoms included behavioral changes (lethargic, loss of equilibrium and disorientation), pale discoloration of the skin and gills or reddened skin, focal or total loss of epidermis, overproduction of mucus on the skin and gills, sunken eyes, hemorrhages of the skin and fins, and fin erosion. During the 35 days of challenge, mortalities began to appear at 12 dpi, then reached a maximum between 21 and 24 dpi (Figure 1). The percentage of total mortality for the Amur mirror carp was 66%.

3.2. Heritability and genetic correlations amongst KHVD resistance and production traits

The estimated heritability for resistance to KHVD was moderate (0.43 ± 0.08) on the observed scale and high (0.72 ± 0.13) on the underlying liability scale. Genetic correlations between KHVD resistance and important production traits were in general statistically insignificant (Table 1 – 4). However, genetic correlation between FC after the second overwintering and KHVD resistance was significantly different from zero and negative (r_g = -0.32 ± 0.14). Likewise, genetic correlations between KHVD resistance and biometrical indices (relative head length, relative body height, relative body width) were negative and significant when the traits were measured during the period before the second winter until market size (Table 3 – 4) and at the edge of significance for RBW at market size (Table 4). On the other hand, intermediate positive and significant genetic correlations were found between KHVD resistance and slaughter yields (log-log residuals of headless carcass yield and fillet yield, respectively) (r_g = 0.37 ± 0.14 and 0.44 ± 0.13, respectively). Phenotypic correlations could not be estimated due to the fact that KHVD resistance and other production traits were measured on different individuals.

4. Discussion

The heritability estimate for resistance to KHVD was high on both observed and the underlying scale (0.43 ± 0.08 and 0.72 ± 0.13, respectively). Ødegård et al. (2010) observed even higher heritability (0.79 ± 0.14) for KHVD resistance on the underlying scale in common carp. In their case probably high overall mortality of challenged fish (6% vs. 34% in our study) and significant survival differences within lower number of full-sib families (91 full-sib families vs. 195 full-sib families) could increase the heritability value. Using a subset of the current data set, heritability of KHVD resistance as measured by survival on the underlying scale for the pedigree and genomic relationship matrix was 0.61 and 0.50, respectively (Palaiokostas et al., 2018). However, we used a different animal model and statistic program that showed a slightly higher pedigree

heritability (0.72). Similar significant heritability estimates of resistance to diseases have been reported, which demonstrated the feasibility of genetic improvement through selection (e.g. Doan Q. et al., 2017; Shoemaker et al., 2017; Barría et al., 2019; Gjerde et al., 2019). More specifically, there is a strong potential to improve resistance to KHVD by a breeding program. Still, it would be very useful to find a reliable way of selecting resistant candidates (to predict KHVD resistance) without challenging the fish to KHV. Furthermore, challenge tests to diseases are problematic with respect to animal welfare and sometimes even to further utilization and rearing of challenged survivor fish as broodstock, which is the cheap but risky solution to select for a disease without need for family information (e.g. KHV is on the list of notifiable diseases, so challenged fish could not be reared in outer pond conditions any more).

In our data, almost all genetic associations between KHVD resistance and production traits were insignificant. Similar to Ødegård et al. (2010) we found no genetic correlation between KHVD resistance and pond survival. So, genetic improvement of KHVD resistance is not genetically related to better general survivability in the absence of disease outbreaks. Similarly, we found insignificant genetic correlations between disease resistance and growth-related traits, as has been found in other fishes (e.g. Silverstein et al., 2009; Yáñez et al., 2014; Flores-Mara et al., 2017; Bassini et al., 2019). This means that selection of fish for growth, the trait typically given the highest weighting in a carp breeding program, should not increase susceptibility of fish to diseases. The absence of significant genetic correlations among commercially important production traits (e.g. growth, % muscle fat, survival) and KHVD in Amur mirror carp suggested that selective breeding program should not affect the resistance of carp to KHVD and vice versa.

Significantly negative genetic correlation was observed between FC after the second overwintering and KHVD resistance, suggesting that selection for lower FC could improve the resistance of fish to that disease. Likewise, RBH, RBW and RHL were significantly negatively

related to KHVD resistance from the second growing season to the third growing season. This is in accordance with the fact that FC in Amur mirror carp is closely genetically related to the body shape and to relative body height and relative head length (Prchal et al., 2018b). So, such associations implied that Amur mirror carp with typically more prolonged body shape of Amur wild scaly carp, which was used to establish Amur mirror carp (Flajšhans et al., 2015), is well known as one of the most resistant carps to KHVD (Piackova et al., 2013). So, selection for lower FC, RHL, RBW or RBH would indirectly increase KHVD resistance probably due to the fact that such fish would bear more genes from wild scaly carp that might be responsible for resistance to KHVD and these genes are linked to those responsible for prolonged body shape or might show certain pleiotropic effect, similarly like scalimess pattern in relation to fitness traits in common carp (Casas et al., 2013). Moreover, such selection could indirectly further improve slaughter yields at market size as there is a relationship that prolonged body shape is genetically related to higher dress out traits in common carp (Prchal et al., 2018a). That is why selection of fish for log-log residuals of slaughter yields could positively affect KHVD resistance and vice versa.

We should also take into consideration that any selection (e.g. for increased KHVD resistance or dress out yield) that might indirectly lead to significant decrease of RHL might also negatively impact the animals welfare. Gills control vital respiration and osmoregulation processes, as such a significant decrease of RHL might impair their function. Moreover, any selection that might indirectly lead to a significant change of less favourable body shape for market acceptance should also be under close monitoring (Haffray et al., 2012; Fraslin et al., 2018; Prchal et al., 2018a). Therefore, further studies are needed to identify real effect of long-term selective breeding program focused on improved KHVD resistance and/or slaughter yields on body shape and allometry.

5. Conclusion

In conclusion, we identified negative genetic correlations between KHVD resistance and body shape traits, and the favorable genetic correlations between KHVD resistance and slaughter yields. In addition, the absence of significant genetic correlations between other production traits and KHVD resistance indicates that selection for improved production traits is not expected to increase the susceptibility of fish to KHVD and vice versa.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Author contributions

MP, DG and MK shared on establishing and on-growing the experimental stock, juvenile phenotyping, PIT tagging, and fin clipping of fish. TV, DP, VP and LP carried out the challenge experiment. JZ, MP, MV, AV, JB, AB, HKK and MK shared on final trait recordings. CP, RH and LG carried out DNA extractions and parentage assignment. MP introduced JZ to the quantitative genetic analysis. JZ and MP estimated the genetic parameters. All authors contributed to drafting the manuscript.

Acknowledgements

This study is part of the FishBoost project, funded by the European Union under the 7th Framework Programme under grant agreement (613611), project of NAAR (NAZV) (QK1910430) under Ministry of Agriculture of the Czech Republic, and projects Biodiversity

(CZ.02.1.01/0.0/0.0/16_025/0007370) and PROFISH (CZ.02.1.01/0.0/0.0/16_019/0000869) both under the Ministry of Education, Youth and Sports of the Czech Republic.

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Figure 1. Daily mortality of fish during the KHV challenge experiment

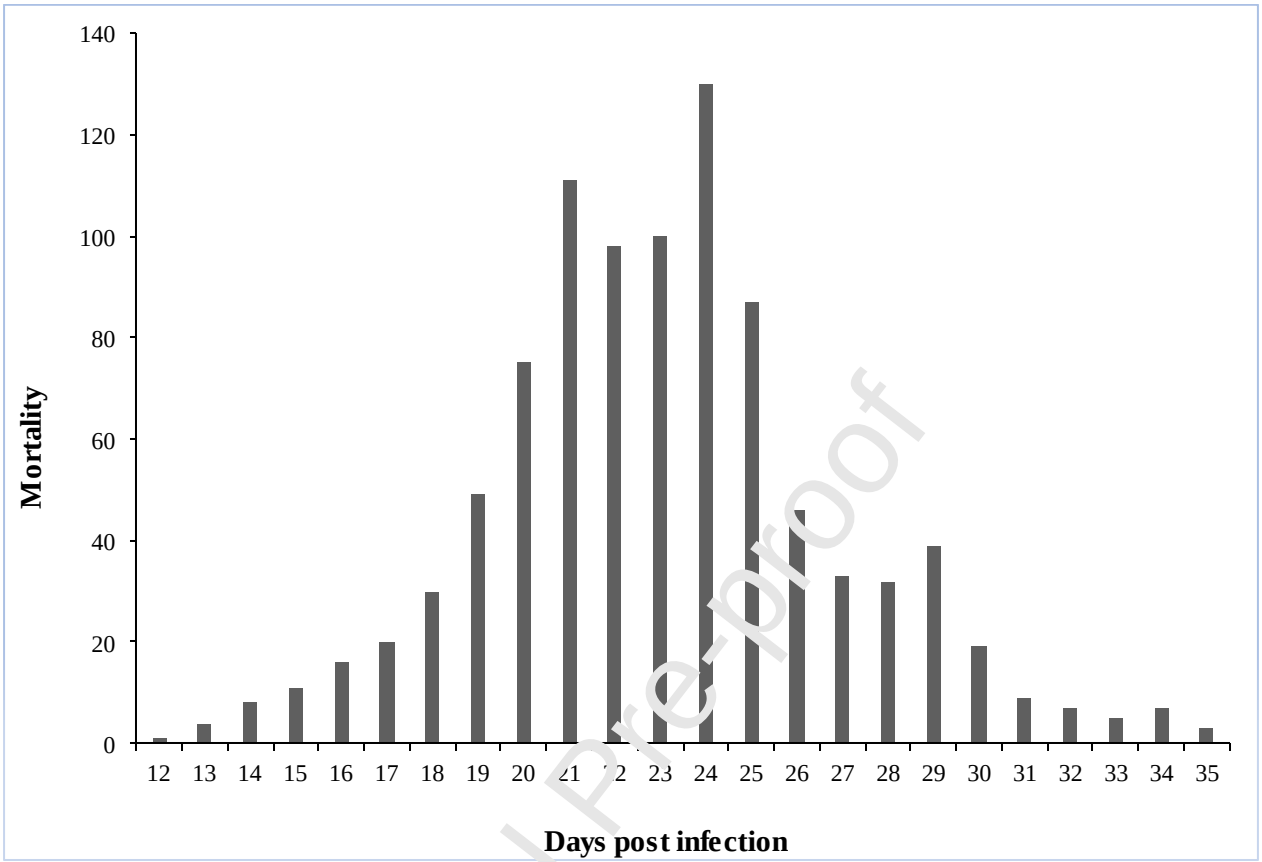

Table 1. Genetic correlations (± standard error) between KHVD resistance and body weight (BW) and condition factor (FC) in challenged fish

	KHVD resistance
BW	-0.02 ± 0.18
FC	-0.16 ± 0.17

Table 2. Genetic correlations (± standard error) between KHVD resistance and production traits of siblings after the first overwintering

	KHVD resistance
BW	0.06 ± 0.18
FC	-0.07 ± 0.17
RBH	-0.26 ± 0.16
RBW	-0.23 ± 0.19
RHL	-0.15 ± 0.21

BW = body weight, **FC** = Fulton's condition factor, **RBH** = relative body height, **RBW** = relative body width, **RHL** = relative head length.

Table 3. Genetic correlations (± standard error) between KHVD resistance and production traits of siblings related to the second overwintering

	KHVD resistance
Fatch	-0.17 ± 0.19
% Fatch	-0.17 ± 0.19
SGR	-0.10 ± 0.17
Winter Surv	-0.19 ± 0.3[illegible]
FC_B	-0.[illegible]8 ± 0.15
FC_A	**-0.32 ± 0.14***
% Fat_B	0.15 ± 0.16
% Fat_A	0.07 ± 0.16
BW_B	-0.07± 0.17
BW_A	-0.05 ± 0.17
RBH_B	**-0.45 ± 0.13***
RBH_A	**-0.35 ± 0.14***
RBW_B	**-0.39 ± 0.15***
RBW_A	**-0.38 ± 0.15***
RHL_B	**-0.39 ± 0.15***
RHL_A	**-0.41 ± 0.14***

B = the trait was recorded before the second overwintering, **A** = the trait was recorded after the second overwintering, **Fatch and % Fatch** = absolute and relative fat change, **SGR** = specific growth rate, **Winter Surv** = winter survival, **FC** = Fulton's condition factor, **% Fat** = muscle fat content, **BW** = body weight, **RBH** = relative body height, **RBW** = relative body width, **RHL**= relative head length. *Confidence limit $|r_g|$ - |1.96 × S.E.| not being zero or less represents significant correlations at $p < 0.05$.

Table 4. Genetic correlations (± standard error) between KHVD resistance and market size production traits of siblings

	KHVD resistance
Market Surv	0.19 ± 0.24
% Fat	0.16 ± 0.15
FC	-0.20 ± 0.14
BW	-0.19 ± 0.15
Logr_hl-Carss	**0.37 ± 0.14***
Logr_Fill	**0.44 ± 0.13***
RBH	**-0.29 ± 0.14***
RBW	-0.26 ± 0.15
RHL	**-0.35 ± 0.14***

Market Surv = market size survival, **% Fat** = muscle fat content, **FC** = Fulton's condition factor, **BW** = body weight, **Logr_hl-Carss** = log-log residuals of headless carcass yield, **Logr_Fill** = log-log residuals of fillet yield, **RBH** = relative body height, **RBW** = relative body width, **RHL**= relative head length. *Confidence limit $|r_g|$ - |1.96 × S.E.| not being zero or less represents significant correlations at $p < 0.05$.

Highlights:

- Heritability for Koi herpesvirus disease (KHVD) resistance was high.
- Most genetic correlations between KHVD resistance and important production traits were insignificant.
- KHVD resistance was significantly genetically correlated to body shape traits and slaughter yields.