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Dissection of X chromosome dosage compensation for quantitative traits in sheep using different statistical models

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Since males and females have different number of X chromosome, different mechanisms have evolved to equalize dosage of gene products from the X chromosome between XX females and XY males. The aim of this study was to study X chromosome dosage compensation for growth rate (GR), Kleiber ratio (KR), efficiency of growth (EF) and relative growth rate (RGR) in Zandi sheep. A two steps procedure was adopted to analysis data. In the first step, each trait was analyzed with a series of 6 animal models including different combinations of direct and maternal effects. Using Akanke's Information Criterion (AIC) the best model (Model I) was selected for each trait. In the second step, five additional models were fitted by adding X chromosome effects to the Model I, considering 5 strategies for modeling X chromosome dosage compensation: (1) no global dosage compensation (ngdc), (2) random inactivation in the homogametic sex (hori), (3) doubling of the single shared sex chromosome in the heterogametic sex (hedo), (4) halving expression of both sex chromosomes in the homogametic sex (hoha) or (5) inactivation of the paternal sex chromosome in the homogametic sex (hopi). Predictive ability of models was measured using the mean squared error of prediction (MSE) and Pearson's correlation coefficient between the real and predicted values of records $(\mathrm{r}(y, \widehat{y}))$. Correlations between traits due to autosomal- and X-linked genetic effects were estimated by bi-variate analyses. For GR and KR, models including X-linked effects lead to a much better fit of data, expressed by the strong decrease in the AIC criterion. Models including X-linked effects had also better predictive ability as they provided smaller MSE and higher $\mathrm{r}(y, \widehat{y})$. For GR and KR, although all strategies for modeling X chromosome dosage compensation improved general properties of the model, the model "ngdc" fitted the data significantly better than other models. Including X-linked genetic effects in the model led to 10% (GR, KR) decrease in the autosomal additive variance, and 7% (KR) to 19% (GR) decrease in the residual variance. Estimates of autosomal heritability (h^2_a), were 0.15 ± 0.03, 0.13 ± 0.03, 0.9 ± 0.03 and 0.13 ± 0.03 for GR, KR, EF and RGR, respectively. X-linked heritability (h^2_s) was 0.08 ± 0.03 for GR and 0.04 ± 0.03 for KR, respectively. Maternal heritability (h^2_m) were 0.02 ± 0.01, 0.01 ± 0.01, 0.03 ± 0.02 and 0.03 ± 0.02 for GR, KR, EF and RGR, respectively. For GR and KR, the Spearman's correlation between breeding values obtained from the best model and model I deviated from unity, indicating re-ranking of top animals across models. The X-linked additive genetic correlation and autosomal additive genetic correlation were similar in terms of sign and magnitude in a way that they were all positive and high. As considering X-linked genetic effects resulted to an improvement in the general properties of the model and possibility of re-ranking of top animals, including these effects in the model, considering dosage compensation on the X chromosome was recommended.

Keywords Sheep, Growth rate, X chromosome, Dosage compensation, Heritability

Abbreviations

GR	Growth rate
KR	Kleiber ratio
EF	Efficiency of growth
RGR	Relative growth rate

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BW	Birth weight
WW	Weaning weight
AIC	Akaike information criterion
ngdc	No global dosage compensation
hori	Random inactivation in the homogametic sex
hedo	Doubling of the single shared sex chromosome in the heterogametic sex
hoha	Halving expression of both sex chromosomes in the homogametic sex
hopi	Inactivation of the paternal sex chromosome in the homogametic sex
BLUP	Best linear unbiased prediction

Lamb growth rate is a key component of profitable sheep farming systems. Faster growing lambs are likely to be slaughtered earlier and/or be heavier at slaughter than their slower growing counterparts and therefore, brings a quicker income to the farmer. More importantly, faster growing lambs are more efficient user of feed because of the lower ratio of maintenance to total feed requirements. A wide range of factors interact to affect lamb growth rate, including ewe live weight and body condition, ewe milking ability, pasture quality and quantity and the genetic ability of the lamb to grow[1]. Since, part of the phenotypic variation in growth rate and efficiency-related traits among animals has genetic origin, this genetic variation can be exploited to improve these traits genetically. However, a genetic improvement program requires knowledge of variance components and genetic parameters to predict selection response, compare breeding plans, and predict the breeding values of selection candidates[2]. The heritability of growth rate and efficiency-related traits has been estimated by several authors including Sing et al.[3], Javanrouh et al.[4] and Mokhtari et al.[5]. However, in most studies, the effects of X chromosome are ignored (see Sing et al.[3] and references therein).

In mammals, sex is determined by the heteromorphic sex chromosomes: XY chromosomes in males and XX chromosomes in females. There are more than 1000 genes on the X chromosome that is virtually identical across species. The Y chromosome is very much smaller, having lost all but a few of these genes and so is relatively gene poor[6]. The SRY gene on the Y chromosome underlies sex determination by initiating testis formation[7]. Most genes on the X chromosome do not have a Y chromosome counterpart and do not have sex-specific functions. Therefore, X copy number in males and females is different. This presents a challenge to placental mammals, who need to (roughly) equalize expression from the X chromosome in male (XY) and female (XX) cells. Deviation from diploidy may induce detrimental consequences. For example, gene duplications or deletions can induce cancer and chromosome monosomy or trisomy usually causes fetal lethality[8]. Ohno[9] suggested upregulation of the X-linked genes in the heterogametic sex (XY) to maintain their expression to the levels of the diploid autosomes. Another mechanism is inactivating one X chromosome in females during early development by assembling a distinctive form of chromatin that largely silences gene expression[10]. Upregulation of the X-linked genes and inactivating one X chromosome in females balance the X chromosome gene dosage between males and females. These mechanisms have been actively studied in mice and humans but lag behind in domestic species[8].

Although suitable approach to construct sex-chromosome additive genetic relationship matrix (**S**-matrix) for using in the mixed animal models to estimate BLUPs of autosomal and X-chromosomal additive effects was developed[11], due to the lack of suitable software, the use of this approach was delayed until recently. By developing software such as WOMBAT[12] and ASReml[13] that were able to consider X-chromosome additive genetic relationship matrix (**S**-matrix) in the animal model framework, several authors including Maraveni et al.[14], Latifi[15], Ghafouri-Kesbi and Abbasi[16], Kargar Borzi[17], Noorian et al.[18] and Bahri-Binabaj et al.[19] estimated the ratio of phenotypic variation in economic traits of sheep which caused by activity of loci on the X chromosome. These authors pointed out that including the X-linked genetic effects in the model of genetic evaluation can help to better understanding of autosomal way of inheritance and to increase the accuracy of genetic evaluation. However, none of these studies considered dosage compensation on the X chromosome for analyzing complex traits of livestock. To inverse **S**-matrix, different mechanisms for dosage compensation on the X chromosome have been proposed including no global dosage compensation, random inactivation in the homogametic sex, doubling of the single shared sex chromosome in the heterogametic sex, halving expression of both sex chromosomes in the homogametic sex, or inactivation of the paternal sex chromosome in the homogametic sex[20]. Linear models in BLUP that separate autosomal and X-linked additive effects and different mechanisms for gene dose compensation can be used to identify significant random effects and effective mechanisms of dosage compensation on the X chromosome[21]. In sheep, the effects of X chromosome dosage compensation on growth and efficiency related traits have not been studied so far. Therefore, the aim of this study was to estimate the autosomal and X-linked genetic components for growth rate and efficiency-related traits in Zandi sheep considering different models for dosage compensation on the X chromosome.

Materials and methods

Data

The phenotype and pedigree data was provided by the Zandi sheep breeding station located in Tehran, Iran. The station was established by the ministry of agriculture of Iran with the aim of improving the whole population of Zandi sheep. The pedigree included 5930 animals distributed over 10 generations (Table 1). The errors in pedigree were detected and corrected using CFC software[22]. The errors were (1) repeated animals in the pedigree (2) animals which were registered as their own sire or dam and (3) presence of loop in the pedigree.

Birth weight (**BW**) and weaning weight (**WW**) were extracted from data files. To account for the differences among animals with different ages, weaning weights were adjusted to standard 90 days. The increase in body weight from birth to weaning was used to calculate growth rate (**GR**) by dividing total gain by the number of days in the period. The estimate of **GR** was then used to calculate the corresponding Kleiber ratio[23] as $\mathbf{KR = GR/WW^{0.75}}$.

No. of generations (including base generation)	10
No. of animals in the pedigree file	5930
No. of base animals	424
No. of non-base animals	5611
No. of animals with progeny	1620
No. of animals without progeny	4310
No. of sires with progeny	170
No. of dams with progeny	1450
No. of grand sire	133
No. of grand dam	752

Table 1. Pedigree structure of the Zandi sheep.

Item	Trait			
	GR(gr)	KR	EF(%)	RGR
No. records	3533	3533	3533	3533
No. of sire with progeny	163	163	163	163
No. of sire with progeny and record	114	114	114	114
Average number of progeny per sire	19.66	19.66	19.66	19.66
No. of dam with progeny	1265	1265	1265	1265
No. of dam with progeny and record	713	713	713	713
Average number of progeny per dam	2.80	2.80	2.80	2.80
Min	53	10	96.75	1.11
Max	295	23	688.20	2.34
Mean	171.87	18.24	379.51	1.72
S.D	42.39	1.93	102.07	0.23
CV (%)	18.59	8.61	26.91	13.37

Table 2. Characteristics of the data structure. **GR** = growth rate; **KR** = Kleiber ratio; **EF** = efficiency of growth; **RGR** = relative growth rate. S.D = standard deviation; CV = coefficient of variation.

Model number	Random effects				
	δ_a^2	δ_c^2	δ_m^2	$\delta_{a,m}$	δ_e^2
1	✓				✓
2	✓	✓			✓
3	✓		✓		✓
4	✓		✓	✓	✓
5	✓	✓	✓		✓
6	✓	✓	✓	✓	✓

Table 3. The random (co)variance components used in the six models. δ_a^2 = autosomal additive genetic variance; δ_c^2 = maternal permanent environmental variance; δ_m^2 = maternal additive genetic variance; $\delta_{a,m}$ = direct-maternal additive genetic covariance; δ_e^2 = residual variance.

Body weights were also used to calculate the efficiency of growth[16] as $\mathbf{EF} = ((\mathbf{WW} - \mathbf{BW})/\mathbf{BW}) \times 100$. In addition, the relative growth rate[24] from birth to weaning (**RGR**) was calculated as $\mathbf{RGR} = \mathrm{Log_e}(\mathbf{WW}) - \mathrm{Log_e}(\mathbf{BW})/90$. Summary statistics of the studied traits are shown in Table 2.

Statistical analysis

Fixed effects including year of birth, age of dam at lambing, sex of lambs and type of birth were analyzed with the GLM function in R[25]. These fixed effects were significant ($p < 0.05$) for all traits and were subsequently included in the linear mixed models.

Estimation of variance components and genetic parameters was done in a two-step process. In the first step, each trait was analyzed with 6 univariate animal models, including various combinations of animal and maternal effects (Table 3). Model 1, which included only random animal effects, was the simplest. On the contrary, Model

6, which was the complete animal model, included animal additive genetic, maternal permanent environmental, maternal additive genetic and direct-maternal additive genetic covariance. The general representation of the Model 6 was as follow:

$$\mathbf{y} = \mathbf{X}\beta + \mathbf{Z_1 a} + \mathbf{Z_2 c} + \mathbf{Z_3 m} + \mathbf{e}, \mathrm{Cov}(\mathbf{a}, \mathbf{m}) = \mathbf{A}\sigma_{\mathrm{a,m}}$$

where **y** is the vector of observations. **β** is the vector of fixed effects fitted with design matrix **X**. $\mathbf{Z}_1$ is the design matrix for animal additive genetic effects. $\mathbf{Z}_2$ and $\mathbf{Z}_3$ are incidence matrices relating observations to maternal permanent environmental and maternal additive genetic effects, respectively. **A** was the numerator relationship matrix and **a**, **c**, **m** and **e** were vectors for direct additive genetic, maternal permanent environmental, maternal additive genetic, and residual effects, respectively. Cov(**a**,**m**) was direct-maternal additive genetic covariance.

To estimate variance components and genetic parameters, the WOMBAT[12] program was used. The information criterion of Akaike[26] (**AIC**) was computed to rank the models according to their power to fit the data. Let p denotes the number of random (co)variance parameters to be estimated, and log L is the maximum log-likelihood, then the information criterion is defined as **AIC** = − 2 log L + 2p. The model yielding the smallest **AIC** fits the data best. Predictive ability of models was measured using the mean squared error of prediction (MSE) and Pearson's correlation coefficient between the real and predicted values of records $(\mathrm{r}(y, \widehat{y}))$.

In the second step, X-linked effects were added to the best model selected in the step one (from now on, referred to as Model **I**). Five models (models 7 to 11) were fitted for considering X chromosome dosage compensation. These models were the same as Model **I** but allowed an X-linked genetic effect as follows:

$$\text{Models 7-11} : \mathbf{y} = \mathbf{I} + \mathbf{Z4}\mathrm{s},$$

The X-linked additive genetic relationship matrix (***S***) and its inverse ($\boldsymbol{S}^{-1}$) were constructed using the *nadiv* package[20] in R software[25]. This package utilizes equations presented in the Fernando and Grossman[11]. The $\boldsymbol{S}^{-1}$ was then supplied externally to WOMBAT software[12] using the GIN option. In order to identify the effective dosage compensation mechanism on the X chromosome, the inverse of the ***S*** was constructed considering different models of dosage compensation[20]: (1) no global dosage compensation (**ngdc**), (2) random inactivation in the homogametic sex (**hori**), (3) doubling of the single shared sex chromosome in the heterogametic sex (**hedo**), (4) halving expression of both sex chromosomes in the homogametic sex (**hoha**) and (5) inactivation of the paternal sex chromosome in the homogametic sex (**hopi**). BLUPs of autosomal additive genetic, X-chromosomal additive genetic, maternal permanent environmental and maternal additive genetic can be obtained using mixed model equations considering covariance matrices of random effects ***a***, ***s***, ***c*** and ***m***. (Co)variance matrix for the random effects was as follow:

$$Var\begin{bmatrix} \boldsymbol{a} \\ \boldsymbol{s} \\ \boldsymbol{c} \\ \boldsymbol{m} \\ \boldsymbol{e} \end{bmatrix} = \begin{bmatrix} \mathbf{A}\delta_{\mathbf{a}}^{\mathbf{2}} & \mathbf{0} & \mathbf{0} & \mathbf{A}\delta_{\mathrm{am}} & \mathbf{0} \\ \mathbf{0} & \boldsymbol{S}\delta_{\mathrm{s}}^{2} & \mathbf{0} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{I}_{\mathrm{c}}\delta_{\mathrm{c}}^{2} & \mathbf{0} & \mathbf{0} \\ \mathbf{A}\delta_{\mathrm{am}} & \mathbf{0} & \mathbf{0} & \mathbf{A}\delta_{\mathrm{m}}^{2} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{I}_{\mathrm{e}}\delta_{\mathrm{e}}^{2} \end{bmatrix}$$

where **a**, **s**, **c**, **m** and **e** are vectors for autosomal additive genetic, X-linked additive genetic, maternal permanent environmental, maternal additive genetic and residual effects, respectively. δ_{a}^{2}, δ_{s}^{2}, δ_{c}^{2}, δ_{m}^{2}, and δ_{e}^{2} are autosomal additive genetic variance, X-linked additive genetic variance, maternal permanent environmental variance, maternal additive genetic variance, and residual variance, respectively. $\sigma_{\mathrm{a,m}}$ was direct-maternal additive genetic covariance. **A** was the numerator relationship matrix and $\mathbf{I}_{\mathbf{c}}$ and $\mathbf{I}_{\mathbf{e}}$ were identity matrices of appropriate dimensions.

Estimated additive breeding values (EBVs) for individuals for studied traits were derived using the best linear unbiased prediction procedure (BLUP). The effect of inclusion of X-linked effects in the model on additive breeding values was tested by estimating the Spearman's correlation between breeding values obtained from the best model and model **I** (best model without X-linked effects). In addition, change in the ranking of top 10 and top 100 animals based on their EBVs obtained from the best model and model **I** was monitored by calculating the number of animals that dropped from the top 10 or top 100 animals after including X-linked effects in the model.

Correlations between traits were estimated by bi-variate analyses. The models applied in the bi-variate analyses were those selected as best for each of the underlying traits in the uni-variate analyses. The matrix notation for the bivariate model was as follow:

$$\begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{X}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{X}_2 \end{bmatrix} \begin{bmatrix} \mathbf{b}_1 \\ \mathbf{b}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{Z}_{\mathbf{a}1} & \mathbf{0} \\ \mathbf{0} & \mathbf{Z}_{\mathbf{a}2} \end{bmatrix} \begin{bmatrix} \mathbf{a}_1 \\ \mathbf{a}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{Z}_{\mathbf{s}1} & \mathbf{0} \\ \mathbf{0} & \mathbf{Z}_{\mathbf{s}2} \end{bmatrix} \begin{bmatrix} \mathbf{s}_1 \\ \mathbf{s}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{Z}_{\mathbf{m}1} & \mathbf{0} \\ \mathbf{0} & \mathbf{Z}_{\mathbf{m}2} \end{bmatrix} \begin{bmatrix} \mathbf{m}_1 \\ \mathbf{m}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \end{bmatrix},$$

where $\mathbf{y}_1$ and $\mathbf{y}_2$ denote traits 1 and 2, respectively.

Trait	$r(y, \widehat{y})$		MSE	
	Model 7	Model I	Model 7	Model I
GR	0.79	0.72	717.21	925.29
KR	0.72	0.68	1.729	1.908
EF	0.65	0.65	5550.23	5586.66
RGR	0.69	0.68	0.0291	0.0301

Table 4. Predictive ability of the best model and model **I** measured by $\mathbf{r}(\boldsymbol{y}, \widehat{\boldsymbol{y}})$ and **MSE**. **GR** = growth rate; **KR** = Kleiber ratio; **EF** = efficiency of growth; **RGR** = relative growth rate. MSE = Mean squared error of prediction; $r(y, \widehat{y})$ = Pearson's correlation coefficient between the real and predicted values of records $(r(y, \widehat{y}))$.

Model	δ_a^2	δ_s^2	δ_m^2	δ_c^2	$\delta_{a,m}$	δ_e^2	δ_p^2	h_a^2	h_s^2	h_m^2	h_c^2	$r_{a,m}$	AIC
1	263.819					1100.85	1364.67	0.19 ± 0.03					14,208.824
2	219.866			66.577		1072.19	1358.63	0.16 ± 0.03			0.05 ± 0.02		14,207.770
[1] 3	210.213		59.898			1093.60	1363.71	0.15 ± 0.03		0.04 ± 0.02			14,206.708
4	220.639		69.440		− 12.911	1086.95	1364.12	0.16 ± 0.03		0.05 ± 0.02		− 0.10 ± 0.15	14,207.660
5	211.693		20.747			1075.88	1359.43	0.16 ± 0.03		0.01 ± 0.02	0.04 ± 0.02		14,206.539
6	221.237		27.386	51.112	− 10.266	1070.05	1359.83	0.16 ± 0.03		0.02 ± 0.02	0.04 ± 0.02	− 0.13 ± 0.17	14,207.544
7 (**I** + **ngdc**)	**188.469**	**94.294**	**26.628**			**889.779**	**1199.17**	**0.15 ± 0.03**	**0.08 ± 0.03**	**0.02 ± 0.01**			**13,926.221**
8 (**I** + **hori**)	189.939	31.918	27.925			900.556	1150.34	0.16 ± 0.03	0.03 ± 0.01	0.02 ± 0.02			13,928.467
9 (**I** + **hedo**)	189.939	31.920	27.925			900.556	1150.34	0.16 ± 0.03	0.03 ± 0.01	0.02 ± 0.02			13,928.467
10 (**I** + **hoha**)	189.939	31.918	27.925			900.556	1150.34	0.16 ± 0.03	0.03 ± 0.01	0.02 ± 0.02			13,928.467
11 (**I** + **hopi**)	187.105	110.817	27.875			842.653	1168.45	0.16 ± 0.03	0.09 ± 0.02	0.10 ± 0.02			13,928.360

Table 5. Estimates of variance components and genetic parameters for growth rate (best model in bold). $\boldsymbol{\delta_a^2}$ = additive genetic variance; $\boldsymbol{\delta_s^2}$ = X-linked additive genetic variance; $\boldsymbol{\delta_m^2}$ = maternal genetic variance; $\boldsymbol{\delta_c^2}$ = maternal permanent environmental variance; $\boldsymbol{\delta_{a,m}}$ = direct-maternal additive genetic covariance; $\boldsymbol{\delta_e^2}$ = residual variance; $\boldsymbol{\delta_p^2}$ = phenotypic variance; $\boldsymbol{h_a^2}$ = additive heritability; $\boldsymbol{h_s^2}$ = X-linked heritability; $\boldsymbol{h_m^2}$ = maternal heritability; $\boldsymbol{h_c^2}$ = maternal permanent environmental effect; $r_{a,m}$ = direct-maternal additive genetic correlation; **AIC** = Akaike's Information Criterion.

Results

In the step one, for all traits studied, model 3 which included direct and maternal additive genetic had the lowest **AIC** and, therefore, selected as the best model (Model **I**). In the step 2, for **GR** and **KR**, adding X-linked effects to the best model already selected in step one (Model **I**), led to a substantially better data fit stated by the significant decrease in the **AIC** values. For **GR** and **KR**, model 7 in which no global dosage compensation (**ngdc**) was used to model X-chromosome dosage compensation was superior to other models expressed by lower **AIC** values. This model had also better predictive ability compared to model **I** as it provided lower MSE and higher $r(y, \widehat{y})$ (Table 4). For **EF** and **RGR**, adding X-linked effects to the model **I**, didn't led to an additional improvement in the likelihood of the model. In addition, regarding measures of predictive ability, there was no superiority over model **I**. Therefore, for **EF** and **RGR**, Model **I** was selected as the final best model.

Tables 5, 6, 7, and 8 present estimates of variance components and genetic parameters for the studied traits. Including X-linked genetic effects in the model led to 10% decrease in autosomal additive genetic variance for **GR** and **KR**. In addition, accounting for X-linked genetic effects in the model decreased residual variance by 19% (**GR**) and 7% (**KR**). Based on the best models, estimates of additive heritability ($\mathbf{h_a^2}$), were 0.15 ± 0.03, 0.13 ± 0.03, 0.9 ± 0.03 and 0.13 ± 0.03 for **GR**, **KR**, **EF** and **RGR**, respectively. X-linked heritabilities ($\mathbf{h_s^2}$) were 0.08 ± 0.03 and 0.04 ± 0.03 for **GR** and **KR**, respectively. Maternal heritability ($\mathbf{h_m^2}$) were 0.02 ± 0.01, 0.01 ± 0.01, 0.03 ± 0.02 and 0.03 ± 0.02 for **GR**, **KR**, **EF** and **RGR**, respectively.

The Spearman's correlation between breeding values obtained from the best model and model **I** was 0.94 for **GR** and 0.95 for **KR.** The number of animals that remained in their cohorts (top 10 and top 100 animals) after including X-linked effects in the model is shown in Table 9. Out of 10 top animals, for **GR** and **KR**, respectively, 7 and 8 animals (on average 8 animals) were common when EBVs of Zandi lambs were estimated using the model **I** and model 7 (**I** + **ngdc**). For 100 top animals, 73 and 78 animals (on average 76 animals) were common, indicating re-ranking of top animals after including X-linked effects in the model.

Table 10 shows correlations between traits. Estimates of X-linked additive genetic correlations ($\mathbf{r_s}$) and autosomal additive genetic correlations ($\mathbf{r_a}$) were all positive and high. Phenotypic correlations between traits were also positive but lower than $\mathbf{r_s}$ and $\mathbf{r_a}$.

Model	δ_a^2	δ_s^2	δ_m^2	δ_c^2	$\delta_{a,m}$	δ_e^2	δ_p^2	h_a^2	h_s^2	h_m^2	h_c^2	$r_{a,m}$	AIC
1	0.403					2.184	2.588	0.16 ± 0.02					3363.25
2	0.373			0.046		2.163	2.584	0.15 ± 0.03			0.02 ± 0.02		3362.98
I 3	0.373		0.131			2.182	2.586	0.14 ± 0.03		0.05 ± 0.02			3361.94
4	0.356		0.110		0.017	2.192	2.585	0.14 ± 0.04		0.04 ± 0.02		0.21 ± 0.24	3362.98
5	0.370		0.081	0.041		2.165	2.584	0.15 ± 0.03		0.03 ± 0.02	0.02 ± 0.02		3362.67
6	0.361		0.079	0.039	0.010	2.171	2.583	0.14 ± 0.04		0.03 ± 0.02	0.02 ± 0.02	0.39 ± 0.28	3363.66
7 (I + ngdc)	**0.337**	**0.100**	**0.022**			**2.023**	**2.483**	**0.13 ± 0.03**	**0.04 ± 0.03**	**0.01 ± 0.01**			**3286.42**
8 (**I + hori**)	0.339	0.033	0.022			2.037	2.433	0.13 ± 0.03	0.01 ± 0.01	0.01 ± 0.02			3287.51
9 (**I + hedo**)	0.339	0.033	0.022			2.037	2.433	0.13 ± 0.03	0.01 ± 0.01	0.01 ± 0.02			3299.80
10 (**I + hoha**)	0.339	0.033	0.022			2.037	2.433	0.13 ± 0.03	0.01 ± 0.01	0.01 ± 0.02			3287.41
11 (**I + hopi**)	0.338	0.107	0.020			1.984	2.454	0.16 ± 0.03	0.04 ± 0.02	0.01` ± 0.02			3287.38

Table 6. Estimates of variance components and genetic parameters for Kleiber ratio (best model in bold). δ_a^2 = additive genetic variance; δ_s^2 = X-linked additive genetic variance; δ_m^2 = maternal genetic variance; δ_c^2 = maternal permanent environmental variance; $\delta_{a,m}$ = direct-maternal additive genetic covariance; δ_e^2 = residual variance; δ_p^2 = phenotypic variance; h_a^2 = additive heritability; h_s^2 = X-linked heritability; h_m^2 = maternal heritability; h_c^2 = maternal permanent environmental effect; $r_{a,m}$=direct-maternal additive genetic correlation; **AIC** = Akaike's Information Criterion.

Model	δ_a^2	δ_s^2	δ_m^2	δ_c^2	$\delta_{a,m}$	δ_e^2	δ_p^2	h_a^2	h_s^2	h_m^2	h_c^2	$r_{a,m}$	AIC
1	820.873					6228.00	7048.88	0.12 ± 0.03					16,960.24
2	645.526			260.130		6120.31	7027.97	0.09 ± 0.03			0.04 ± 0.02		16,958.93
I 3	**613.263**		**228.993**			**6197.85**	**7040.11**	**0.09 ± 0.03**		**0.03 ± 0.02**			**16,957.44**
4	621.721		238.153		− 13.739	6191.95	7040.09	0.09 ± 0.03		0.03 ± 0.02		− 0.04 ± 0.39	16,958.74
5	603.218		135.129	144.373		6147.47	7030.18	0.09 ± 0.03		0.02 ± 0.02	0.02 ± 0.02		16,958.38
6	623.819		149.360	147.183	− 25.080	6134.91	7030.25	0.09 ± 0.03		0.02 ± 0.02	0.02 ± 0.02	− 0.08 ± 0.46	16,959.37
7 (I + ngdc)	551.063	21.198	275.58			6149.76	6997.31	0.08 ± 0.02	≈0.00	0.04 ± 0.02			16,959.63
8 (**I + hori**)	550.451	16.501	276.33			6138.28	6981.56	0.08 ± 0.03	≈0.00	0.04 ± 0.02			16,958.93
9 (**I + hedo**)	550.451	16.501	276.33			6138.28	6981.56	0.08 ± 0.03	≈0.00	0.04 ± 0.02			16,959.86
10 (**I + hoha**)	553.141	0.008	273.96			6163.94	6991.06	0.08 ± 0.03	≈0.00	0.04 ± 0.02			16,959.75
11 (**I + hopi**)	553.141	0.008	273.96			6163.94	6991.06	0.08 ± 0.03	≈0.00	0.04 ± 0.02			16,959.96

Table 7. Estimates of variance components and genetic parameters for efficiency of growth (best model in bold). δ_a^2 = additive genetic variance; δ_s^2 = X-linked additive genetic variance; δ_m^2 = maternal genetic variance; δ_c^2 = maternal permanent environmental variance; $\delta_{a,m}$ = direct-maternal additive genetic covariance; δ_e^2 = residual variance; δ_p^2 = phenotypic variance; h_a^2 = additive heritability; h_s^2 = X-linked heritability; h_m^2 = maternal heritability; h_c^2 = maternal permanent environmental effect; $r_{a,m}$ = direct-maternal additive genetic correlation; **AIC** = Akaike's Information Criterion.

Discussion

Genetic analysis of complex traits in mammals is frequently limited to autosomes, with the X chromosome excluded because of its hemizygosity in males. Broman et al.[27] developed a method for appropriate treatment of the X chromosome for QTL mapping in experimental crosses. Accordingly, some efforts focused on determination of the QTLs on the X chromosome underlying economic traits in livestock. These studies demonstrated the importance of the X chromosome in the genetic determinism of complex traits in livestock and highlighted new functional candidate genes and variants for these traits[28] (see for example Sanchez et al.[28]).

Among strategies used to model dosage compensation on the X chromosome, a model including no global dosage compensation on the X chromosome (**ngdc**) fitted the data best. Dosage regulation of the sex chromosomes can be viewed as either global, i.e. employing mechanisms that modify most—but not all—genes on an entire chromosome, or local, i.e. acting on individual genes. This distinction is somewhat fluid as the number of dosage-compensated genes on a given sex chromosome varies between tissues, and also depends on methods of analysis[29]. Our results showed lack of mechanisms that modify all genes on the X chromosome and, therefore, dosage compensation in sheep may be partial, i.e., not all genes on the X chromosome in females are modified. Nevertheless, to have a clear cut verdict about this finding, more research is needed.

In partial compensation, the male: female ratios of X-linked gene expression vary between 1 (full compensation) and 2 (absence of compensation)[30]. Both complete and partial compensation have been evidenced in different species. Complete dosage compensation by upregulation of the male X chromosome in Drosophila

Model	δ_a^2	δ_s^2	δ_m^2	δ_c^2	$\delta_{a,m}$	δ_e^2	δ_p^2	h_a^2	h_s^2	h_m^2	h_c^2	$r_{a,m}$	AIC
1	0.0060					0.0347	0.0408	0.15 ± 0.03					− 3956.99
2	0.0054			0.0010		0.0344	0.0409	0.13 ± 0.03			0.02 ± 0.02		− 3957.08
I 3	**0.0054**		**0.0013**			**0.0347**	**0.0410**	**0.13 ± 0.03**		**0.03 ± 0.02**			**− 3960.95**
4	0.0065		0.0014		− 0.0012	0.0340	0.0408	0.16 ± 0.04		0.02 ± 0.02		− 0.41 ± 0.22	− 3959.02
5	0.0054		0.0012	0.0010		0.0344	0.0419	0.13 ± 0.03		0.02 ± 0.02	0.02 ± 0.02		− 3959.45
6	0.0066		0.0010	0.0010	− 0.0013	0.0337	0.0413	0.16 ± 0.04		0.02 ± 0.02	0.02 ± 0.02	− 0.45 ± 0.24	− 3959.41
7 (**I + ngdc**)	0.0042	0.0011	0.0010			0.0341	0.0413	0.10 ± 0.02	0.02 ± 0.02	0.02 ± 0.01			− 3941.13
8 (**I + hori**)	0.0043	0.0010	0.0010			0.0346	0.0417	0.13 ± 0.03	0.02 ± 0.02	0.02 ± 0.01			− 3937.72
9 (**I + hedo**)	0.0041	0.0010	0.0010			0.0346	0.0417	0.13 ± 0.03	0.02 ± 0.02	0.02 ± 0.01			− 3937.72
10 (**I + hoha**)	0.0043	0.0010	0.0010			0.0346	0.0417	0.13 ± 0.03	0.03 ± 0.02	0.02 ± 0.01			− 3937.83
11 (**I + hopi**)	0.0042	0.0011	0.0010			0.0335	0.0408	0.13 ± 0.03	0.02 ± 0.02	0.02 ± 0.01			− 3937.23

Table 8. Estimates of variance components and genetic parameters for relative growth rate (best model in bold). δ_a^2 = additive genetic variance; δ_s^2 = X-linked additive genetic variance; δ_m^2 = maternal genetic variance; δ_c^2 = maternal permanent environmental variance; $\delta_{a,m}$ = direct-maternal additive genetic covariance; δ_e^2 = residual variance; δ_p^2 = phenotypic variance; h_a^2 = additive heritability; h_s^2 = X-linked heritability; h_m^2 = maternal heritability; h_c^2 = maternal permanent environmental effect; $r_{a,m}$ = direct-maternal additive genetic correlation; **AIC** = Akaike's Information Criterion.

Trait	Top 10	Top 100
GR	7	73
KR	8	78
Overall mean	≈8	≈76

Table 9. The number of animals that were common between the best model and model **I** based on their additive breeding values. **GR** = growth rate; **KR** = Kleiber ratio.

Trait 1	Trait 2	r_a	r_s	r_p
GR	**KR**	0.88 ± 0.14	0.91 ± 0.27	0.67 ± 0.02
	EF	0.76 ± 0.09		0.44 ± 0.02
	RGR	0.82 ± 0.13		0.39 ± 0.01
KR	**EF**	0.67 ± 0.08		0.43 ± 0.01
	RGR	0.76 ± 0.12		0.21 ± 0.01
EF	**RGR**	0.64 ± 0.10		0.53 ± 0.01

Table 10. Correlations between studied traits. r_a = autosomal additive genetic correlation; r_s = X-linked additive genetic correlation; r_p = phenotypic correlation. **GR** = growth rate; **KR** = Kleiber ratio; **EF** = efficiency of growth; **RGR** = relative growth rate.

melanogaster[31], while in another insect, Heliconius butterfly, there is only partial dosage compensation[32]. In a plant (*Silene latifola*) with newly evolved sex chromosomes no global dosage compensation between sexes was detected[33]. In addition, in chicken, Kaviani et al.[21] analysed body weight at different ages with models similar to ours, and selected a model with no global dosage compensation on the X chromosome as best model for body weights at 8 and 12 weeks of age.

Estimation of the proportions of heritability due to autosomes and X chromosome for economic traits in sheep has a short history, beginning in 2018. Latifi[15] in Mehraban sheep reported estimates of $\mathbf{h}_s^2$ for **GR** and **KR** as 0.10 and 0.07, respectively. In Kermani sheep, Kargar-Borzi[17] reported estimates of $\mathbf{h}_s^2$ as 0.03 and 0.01 for **GR** and **KR**, respectively. For **EF**, Noorian et al.[18] reported estimated value of $\mathbf{h}_s^2$ as 0.02. In addition, for body weight at different ages, estimates of $\mathbf{h}_s^2$ ranged from 0.01 for body weight at birth in Baluchi sheep[19] to 0.14 for body weight at 6 months of age in Lori-Bakhtiari sheep[14]. Our findings, together with previous reports, show that part of phenotypic variation in growth- and efficiency-related traits in sheep caused by the activity of genes on the X chromosome. Therefore, a decrease in the autosomal additive genetic variance was expected after distangling this effect. However, our results showed that by including X-linked effects, not only autosomal additive genetic variance but also residual variance decreased which is an evidence for improvement in the general properties of the model. Our results are in agreement with Larsen et al.[34] who reported 31% decrease in δ_a^2 following inclusion of X-linked genetic effects in the model for plumage spot diameter in barn owls. In

addition, Noorian et al.[18] who worked on efficiency of growth in Baluchi sheep reported 20% decrease in the additive genetic variance when X-linked effects were included in the model.

Ghafouri-Kesbi and Abbasi[16] reported that inclusion of X-linked genetic effects in the animal models when they are really present resulted to increase in the accuracy of genetic evaluation. Information in the Table 9 shows that out of top 10 animals, about 20% of them were dropped from the group when the X chromosome effect was included in the model. It was 25% for top 100 animals, i.e., ranking of top animals will be changed by including X-linked effects in the genetic evaluation model in agreement with Vatankhah et al.[35], who reported that animal models that were able to partition X-linked effects from total additive genetic variation could enable more effective genetic selection to improve economic traits in sheep.

The estimated value of $\mathbf{h}_{\mathbf{a}}^2$ for pre-weaning **GR** (0.15) was in the reported range from 0.03 in the Sangsari breed[36] to 0.42 in the Moroccan Timahdit breed of sheep[37]. For pre-weaning **KR**, literature estimates of $\mathbf{h}_{\mathbf{a}}^2$ ranged from 0.04 in the Arman breed[5] to 0.17 in the Makuei sheep[38]. For pre-weaning **EF**, literature estimates of additive heritability ranged from 0.05 in the Arman breed[4] to 0.07 in the Moghani sheep[39]. For pre-weaning **RGR**, literature estimates of $\mathbf{h}_{\mathbf{a}}^2$ ranged from 0.06 in the Arman breed[18] to 0.15 in the Afshari breed[40]. These reports show that efficiency-related traits have low heritability which means that response to selection will be limited. However, since these traits have a significant influence on the profitability of sheep production, genetic improvement in these traits should be considered.

Genetic correlation is an informative metric to quantify the overall genetic similarity between complex traits, which provides insights into their polygenic genetic architecture. There are no reports on the estimates of the X-linked additive genetic correlation ($\mathbf{r}_s$) for growth- and efficiency-related traits in sheep which makes it impossible to compare the results. However, estimates of the autosomal additive genetic correlation ($\mathbf{r}_a$) were close to those reported by Ghafouri-Kesbi and Gholizadeh[41], Jafaroghli et al.[39] and Javanrouh et al.[4]. Surprisingly, the X-linked additive genetic correlation ($\mathbf{r}_s$) and autosomal additive genetic correlation were similar in terms of sign and magnitude. Positive $\mathbf{r}_a$ and $\mathbf{r}_s$ shows that two traits share similar genes on autosomal and X chromosomes. Strong $\mathbf{r}_a$ and $\mathbf{r}_s$ between **GR** and **KR** indicate that animals with higher **GR** are also efficient user of feed and vice versa, and that this positive $\mathbf{r}_a$ and $\mathbf{r}_s$ between traits guarantee the success of multi-trait selection programs including growth rate and efficiency-related traits.

Conclusions

X-linked genetic effects contributed to phenotypic variation of studied traits up to 8%. Among strategies tested to model dosage compensation on the X chromosome, no global dosage compensation (**ngdc**) strategy was superior to other strategies, possibility indicating partial dosage compensation on the X chromosome. Estimates of X-linked additive genetic correlation indicated that **GR** and **KR** share similar genes on the autosomal and X chromosomes. Since inclusion of X-linked effects in the genetic evaluation model lead to a substantially better data fit, using a model including X-linked effects for estimating variance components and prediction of breeding values was recommended. Nonetheless, as our study was the first attempt to investigate X chromosome dosage compensation in sheep, further research is needed to validate our findings.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

F.G.-K.: conceptualization, methodology, investigation, formal analysis, and writing-original draft. M.E.: conceptualization, investigation, writing-original draft. All authors reviewed the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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