Detecting Major Genes Controlling Robustness of Chicken Body Weight Using Double Generalized Linear Models

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Abstract

Detecting both the majors genes that control the phenotypic mean and those controlling phenotypic variance has been raised in quantitative trait loci analysis. In order to mapping both kinds of genes, we applied the idea of the classic Haley-Knott regression to double generalized linear models. We performed both kinds of quantitative trait loci detection for a Red Jungle Fowl x White Leghorn F2 intercross using double generalized linear models. It is shown that double generalized linear model is a proper and efficient approach for localizing variance-controlling genes. We compared two models with or without fixed sex effect and prefer including the sex effect in order to reduce the residual variances. We found that different genes might take effect on the body weight at different time as the chicken grows.

Key words: variance-controlling genes, quantitative trait loci, double generalized linear models.

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Detecting both the majors genes that control the phenotypic mean and those controlling phenotypic variance has been raised in quantitative trait loci analysis. In order to mapping both kinds of genes, we applied the idea of the classic Haley-Knott regression to double generalized linear models. We performed both kinds of quantitative trait loci detection for a Red Jungle Fowl $\times$ White Leghorn F2 intercross using double generalized linear models. It is shown that double generalized linear model is a proper and efficient approach for localizing variance-controlling genes. We compared two models with or without fixed sex effect and prefer including the sex effect in order to reduce the residual variances. We found that different genes might take effect on the body weight at different time as the chicken grows.

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INTRODUCTION

Detecting both the majors genes that control the phenotypic mean and those controlling phenotypic variance has been raised in quantitative trait loci analysis. In this thesis, we use a statistical method to link certain complex phenotypes to specific regions on chromosomes. We mainly discuss which major genes control the expected mean of the phenotypes, and try to find out whether some major genes control the phenotypic variance.

Background

In this part, we briefly introduce basic terminologies and some principles of genetics.

Gene and Chromosome *Genes*, the DNA fragment of genetic effect, is the basic genetic units, which are used to control biological traits. Genes appear in pairs all the time and regularly transmit unchanged from generation to generation.

Genes are generally very numerous, and situated within the cell nucleus, where they lie in linear order along microscopic bodies called *chromosomes*. The chromosomes also occur in pairs, and the number of pairs is constant for each species (Wu *et al*. 2007). Such as, the pig has 19 pairs of chromosomes, chicken has 39, humans have 23 and so on.

The gene pair located a certain place on specific chromosome. Using genetic markers along the chromosomes, computational and statistical methods can be used to find the locations of genes controlling a particular phenotypic trait.

Meiosis *Meiosis* is a special process of division which is to appear in the production process of germ cells. Unlike *mitosis* when a cell splits into two identical copies, meiotic germ cells produced half the chromosome number (Figure 1). The meiosis can be

divided into three steps. The first step of meiosis is to duplicate the chromosomes and DNA, and the respective numbers of DNA become into twice of ordinary cells. The second step is named first meiotic division, that is the copy of chromosomes pairing alignment at equator of spindle; and the copy of chromosome strands stay together; members of each individual toward poles. Finally the third step is called second meiotic division, that is DNA is not reproduced, but former copy of chromosomes separate now. The cell forms into two identical cells which have half of the number of chromosomes and DNA. Crossing-over, or genetic recombination, can happen after the chromosomes are duplicated, which makes localizing genes on chromosomes possible.

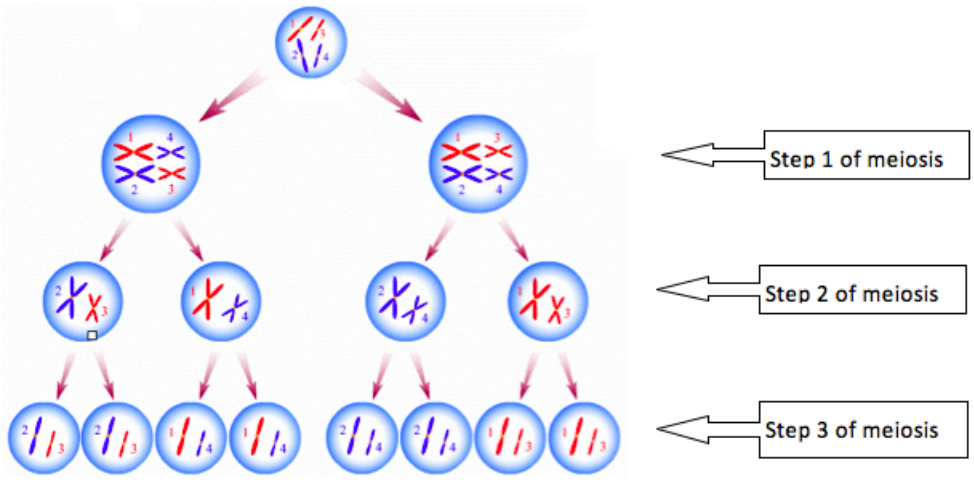

Figure 1: **Meiosis**. Red and blue chromosomes represent copies inherited from father and mother, respectively. Crossing-over is not shown in this figure, but it can happen at step 1 after duplication of the chromosomes.

Mendel's Laws Gregor Johann Mendel, father of modern genetics, had found the two most basic laws of modern genetics. Mendel's first law, also can be called the

law of segregation, is that only one of the two genes controlling a certain character is present in each gamete. According to the meiosis, we can know that the gametes have only one gene from any given pair. For example, if the parental strains have genotype AA, all the gametes that they produce are of type A. If the genotype is Aa, the gametes may have two possible types, A and a. Mendel's second law is named as the *law of independent assortment*. It says that when two or more pairs of genes segregate simultaneously, they do so independently. Suppose that we have two pairs of genes Aa and Bb. Based on the first law, we can know that the gametes have four types - AB, Ab, ab, and aB. Combining these four types of gametes, it can leads to 16 combinations.

Linkage Let us consider an example. There is the formation of gametes by genotype $AaBb$. The loci for the gene pairs Aa and Bb lie on the homologous chromosomes. And one chromosome contains A and B, the other contains a and b. Whether A will be transmitted together with B or b depends on their closeness. If the two genes locate close on the chromosome, the probability that a crossing-over happens between the two genes will be quite small. Such a phenomena is called the genetic *linkage* (Figure 2).

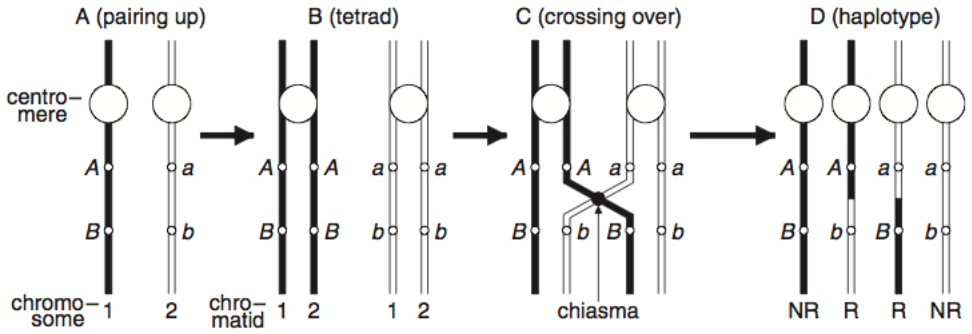

Figure 2: **Diagram for crossing-over between two linked loci** (Wu *et al.* 2007).

Each gamete receives one chromatid from a tetrad to make up the haploid complement (Figure 2 D). Since it is possible that more than one crossing-over occurs on the chromosomes, some chromosomes in the haploid complement consist of a number of segments from the two parental chromosomes. The number of segments is determined by the number of crossing-overs that occurred in the formation of the chromatid that became the chromosome. If no crossing-overs occur, then the chromosome will be a replicate of an entire parental chromosome. If one crossing-over occurs between two loci, the chromosome will consist of two segments, one from each parental chromosome. In the former case, the resultant gametes must be just like the parental chromosomes. In the latter case, where there is one point of crossing-over, we have the new combinations called recombinant types. In general, if there are an even number of points of crossing-overs between the two loci, the chromatids will be like parental types. But if there are an odd number of points of crossing-overs, the chromatids will be recombinant types.

Literature Review

Quantitative trait loci (QTL) analysis is a statistical method that links two types of information, which are phenotypic data and genotypic data. HALEY and KNOTT (1992); MARTÍNEZ and CURNOW (1992) have found a powerful tool to detect QTL controlling the mean of a complex trait in experimental crosses. FALCONER and MACKAY (1996); KEARSEY (1998); LYNCH and WALSH (1997) have been attempted to explain the genetic basis of variation in complex traits with QTL. LYNCH and WALSH (1997) introduced a variety of methods for QTL mapping.

QTL analysis usually concerns the detection of majors genes which control the expected mean of a phenotype. However, there has been evidence indicating that there are genes controlling the phenotypic variance due to sensitivity to environmental ef-

fects. SORENSEN and WAAGEPETERSEN (2003) found that the environmental variance of pig litter size could be under genetic control, and IBANEZ-ESCRICHE *et al.* (2008) also gave the strong evidence that the variance of rabbit litter size is under genetic control. ROWE *et al.* (2006) found that there are large differences when it generates the variance of chicken body weight variance. HILL and ZHANG (2004) have explained that genotypes which associate with higher environmental variance have a greater chance of being selected under directional selection. Such QTL are referred to as variance-controlling QTL or vQTL (RÖNNEGÅRD and VALDAR 2010).

ANDERSSON (2001) expected to find vQTL in experimental crosses between wild and domestic animals. ORDRS *et al.* (2008) studied morphological traits and flowering time in maize. WITTENBURG *et al.* (2009) examined the sample variance of birth weight within pig litters as a gamma distributed trait among 3914 sows. These studies have explicitly looked for vQTL.

Aim of This Paper

The aim of this paper is to use double generalized linear models (DGLMs) to detect major genes controlling the mean of a phenotype and the phenotypic variance. The linear predictors in the DGLMs are specified under the framework of Haley-Knott regression. We also try to compare the models with or without the sex factor.

METHODS

QTL Analysis

QTL analysis is a statistical method that links two types of information - phenotypic data (trait measurements) and genotypic data (usually molecular markers) - in an attempt to explain the genetic basis of variation in complex traits. QTL analysis allows researchers in fields as diverse as agriculture, evolution, and medicine to link certain

complex phenotypes to specific regions of chromosomes. The goal of this process is to identify the action, interaction, number, and precise location of these regions (MILES and WAYNE 2008).

To carry out QTL analysis, it requires parental strains that differ genetically for the trait. The parental strains are crossed, resulting in heterozygous (F1) individuals, and these individuals are then crossed using one of a number of different schemes, for instance, backcross (BC) or an F2 intercross design. Then the phenotypes and genotypes of the derived population are scored. Finally, markers that are genetically linked to a QTL influencing the trait of interest will segregate more frequently with trait values, whereas unlinked markers will not show significant association with phenotype. MACKAY (2001) nicely explained the process of conducting QTL analysis.

In regression based QTL detection methods, we consider the simplest case of two founder lines A and B, and the linear regression model is given by

$$y = X\beta + xa + e \tag{1}$$

Where y is the phenotypic value, X is a design matrix for non-genetic fixed effects and β is the vector including the corresponding fixed effects. And a is the additive effect of the QTL. The covariate x is calculated for each individual i as

$$\begin{aligned} x_i &= \frac{1}{2}(\mathcal{P}(\text{maternal allele is inherited from line A}) \\ &\quad +\mathcal{P}(\text{paternal allele is inherited from line A})) \end{aligned} \tag{2}$$

And e is the random error, typically assumed to be normally distributed as $N(0, \sigma^2)$. QTL detection is done with a plot of a certain statistic measuring the goodness of fit of the models at all the test loci. F-statistic or minus logarithm of p-value are usually used for genome-wide scan. The QTL positions are located near the highest values of the test statistic above the significance threshold. These QTL are putative chromosomal regions harboring major genes controlling the mean of the studied trait. Instead of us-

ing only-marker means, maximum likelihood (ML) method uses the full information from the marker-trait distribution so that is expected to be more powerful. We assume that the distribution of phenotypes for an individual with QTL genotype Q_k is normal with mean μ_k and variance σ^2. The likelihood for an individual with phenotypic value y and marker genotype M_j is

$$\ell(y|M_j) = \sum_{k=1}^{N} \varphi(y, \mu_k, \sigma^2)\mathcal{P}(Q_k|M_j) \tag{3}$$

where $\varphi(y, \mu_k, \sigma^2)$ denotes the density function for a normal distribution with mean μ_k and variance σ^2, and a total of N QTL genotypes are assumed.

In the likelihood framework, tests of whether a QTL is linked to the markers under consideration are based on the likelihood-ratio statistic

$$\lambda = -2\log\left(\frac{\max \ell(y)}{\max \ell_0(y)}\right) \tag{4}$$

where $\ell_0(y)$ is the likelihood under the null hypothesis assuming no QTL effects exist.

Haley-Knott Regression

HALEY and KNOTT (1992) provided a simple regression procedure that gives an excellent approximation of the likelihood map for ML interval mapping. In this procedure, we define that the genetic effect of genotypes QQ, Qq and qq are $\mu + a$, $\mu + d$ and $\mu - a$, respectively, where μ is a mean of genetic effect, a is the deviation of additive effect, and d is the deviation of dominance effect. Haley-Knott regression is conducted as the regression model

$$y_j = \mu + a \cdot x_a(M_j) + d \cdot x_d(M_j) + e_j \tag{5}$$

Taking the expectation over all individuals with marker genotype M_j gives

$$\mu_{M_j} = \mu + a \cdot x_a(M_j) + d \cdot x_d(M_j) \tag{6}$$

We also have

$$\mu_{M_j} = (\mu + a)\mathcal{P}(QQ|M_j) + (\mu + d)\mathcal{P}(Qq|M_j) + (\mu - a)\mathcal{P}(qq|M_j) \quad (7)$$

$$= \mu + a \cdot [\mathcal{P}(QQ|M_j) - \mathcal{P}(qq|M_j)] + d \cdot \mathcal{P}(Qq|M_j) \quad (8)$$

so that

$$x_a(M_j) = \mathcal{P}(QQ|M_j) - \mathcal{P}(qq|M_j) \quad (9)$$

$$x_d(M_j) = \mathcal{P}(Qq|M_j) \quad (10)$$

Therefore, having calculated genotype probabilities at each test locus, genome-wide QTL scan can be carried out using regression model (5).

For calculating the genotype probabilities at all the test loci, we used a recently published software `cnF2freq` (NETTELBLAD *et al.* 2009). This software is implemented in C++ and infers genotype probabilities using a hidden Markov model. It deals with any outbred F2 intercross and includes the pedigree structure in the calculation.

Double Generalized Linear Model

In a generalized linear model (GLM; MCCULLAGH and NELDER 1989), if we observe $y_1, y_2, \ldots, y_n$ as response, we will have $\mu_i = E(y_i)$ and $g(\mu_i) = x_i^T\beta$, where $g(.)$ is a monotonic link function, x_i is a vector of covariates and β is a vector of parameters. Under the GLM assumption, the distribution of y can be written as

$$f(y;\theta,\phi) = \exp\left(\frac{y\theta - b(\theta)}{a(\phi)} - c(y,\phi)\right) \quad (11)$$

where θ is the canonical parameter, and ϕ is the dispersion parameter. From the expression of distribution of y, we can derive that $\mu_i = E(y_i) = b'(\theta)$, $Var(y_i) = \phi b''(\theta)$. $b''(\theta)$ is called the variance function, $V(\mu_i)$, so $Var(y_i) = \phi V(\mu_i)$. This equation describes the relationship between the mean and variance of the response.

The dispersion parameter ϕ can be further modeled, i.e. $Var(y_i) = \phi_i V(\mu_i)$, where ϕ_i is the dispersion parameter of the i:th observation. These dispersion parameters can be modeled as

$$h(\phi_i) = z_i^T \lambda \tag{12}$$

Where $h(.)$ is another link function, z_i is a vector of covariates of dispersions and λ is another vector of parameters. So we get the second layer model, from which we can see the relationship between dispersion parameter and linear predictor.

Now we get two layers of models, the first for the mean and the second for the dispersion, which is a DGLM. We can see the affecting factors for the mean and dispersion at the same time. In this paper, we want to detect which genes control the body weight of chicken, and which genes control the robustness of chicken body weight. DGLM is therefore a good tool for this purpose. The R (R DEVELOPMENT CORE TEAM 2009) package **dglm** was used in our study to fit DGLMs.

QTL Scan Using DGLM

In this paper, we try to detect the genes controlling the mean and variance of chicken body weight, i.e. the mean-controlling QTL and the variance-controlling QTL (vQTL). The scan for QTL and vQTL were done simultaneously using DGLMs. Minus logarithm of the p-value for the additive genetic effect was used as the QTL scan statistic. The mean and dispersion models can be tested separately because the estimates of mean model and variance model are orthogonal (SMYTH 2002).

The hypothesis test for the existence of a QTL on a given chromosome can be written as

$$H_0 : \text{no QTL exists on the chromosome}$$

versus

$$H_1 : \text{at least one QTL exists on the chromosome}$$

Under the null hypothesis, there is no QTL on the chromosome, so there is no link between the phenotypes and the genotypes. Therefore, permutation test can be performed to approximate an empirical extreme-value distribution of the test statistic (the maximum of minus logarithm of p-values for each permutation). In our study, a 95% significance threshold was determined from this distribution. The peaks higher than the significance threshold were picked up as detected QTL or vQTL.

Data Description

The data that we analyzed was from a Red Jungle Fowl $\times$ White Leghorn F2 cross. In this chicken pedigree, one Red Jungle Fowl male was mated to three White Leghorn females, producing 756 F2 offspring with measured marker genotypes and phenotypes. We used an updated marker map to those reported in KERJE *et al.* (2003), including 439 markers, covering chromosomes 1 to 28. The body weights of the F2 individuals at the 1st day, 8th day, 46th day, 112th day and 200th day were recorded, which are the phenotype records we used as responses in our models. Table 1 and Figure 3 give an overview of the phenotypic records.

From Table 1 and Figure 3, we can find that the variances of weights become larger and larger during the growth of the chicken. Different genotypes can have effects on the body weight. Besides genotypes that affect the body weight, many environmental factors can also affect the body weight, such as weather, living environment, food supply and so on. All of these factors can affect the body weight of the chicken.

Table 1: **Summary of the body weight records at five time points.**

Statistic	1st day	8th day	46th day	112th day	200th day
Min	25.7	25.2	172.4	341.2	451.1
25% Quantile	34.6	43.8	278.0	782.6	1073.3
Median	37.3	47.8	311.4	902.8	1258.5
Mean	37.2	47.6	315.1	924.2	1280.4
75% Quantile	39.7	51.5	346.4	1053.0	1482.3
Max	49.6	66.9	481.9	1522.8	2078.9
Variance	13.9	36.2	2977.9	35918.8	71372.2

Data Checking

For the purpose of determine the family of response, we check the responses to see whether it satisfies the normality assumption (Figure 4). We can see that ignoring the scatters at the beginning and the end, the five sets of responses are all approximately normal. So for the mean model, we can choose Gaussian distribution as `family` in **dglm**.

The first layer of our model is (which is also referred to as the mean model)

$$y_i = \mu + x_{i|j}a + e_{i|j} \tag{13}$$

where $x_{i|j}$ is the coefficient of the additive genetic effect a for individual i, i.e. the conditional probabilities given the test locus j. Note that this model only considers the additive genetic effect. μ is an intercept, and $e_{i|j}$ is the normally distributed error term.

The second layer of the model, which is also referred to as the dispersion model, has a linear predictor $\mu^* + x_{i|j}a^*$. The response for this model is ϕ_i, which is the deviance residual of the mean model. It can be derived that the mean and variance of ϕ_i

satisfy $E(\phi_i) = \sigma^2$ and $Var(\phi_i) = 2\sigma^4$. According to the assumption of GLM, a Gamma GLM can be used to fit the dispersion model.

RESULTS

QTL Analysis with No Fixed Effect

From Figure 5, we can find that in different time period, the controlling gene is different, that is, as the chicken grows, some genes loses or stops their effects, and some other genes become active for this trait.

When the chicken was born, there are many factors affecting the body weight, such as the temperature, incubation time and even the matrices condition. From the 8th day of age, the locus around 100 cM becomes active for the body weight of chicken. So we can think that the gene is stably effective after one week of age. In genomic selection, chickens with the genotype at this locus leading to large body weight should be selected. But the genes controlling the variance of the body weight are not always the same one. It shows obviously that from the 46th day to the 112th day of age, the effect of the locus around 500 cM become more and more significant. It means that this locus becomes more and more effective for controlling the robustness of the body weight. Therefore in genomic selection, we may try to select the chicken with large and also robust body weight. The body weight of such a chicken should be less sensitive to the environmental conditions.

QTL Analysis with Fixed Sex Effect

An important factor was ignored in the previous subsection, that is, the sex effect. We know that the body weights of different sexes can differ a lot for chickens and also other animals. Table 2 shows the summary of body weights for male and female chickens in our data.

Table 2: **Summary of the body weights for different sexes.**

Time Point	Mean Body Weight (g)	
	Female	Male
1st day	37.13	37.33
8th day	47.32	47.82
46th day	294.27	337.17
112th day	788.47	1065.54
200th day	1079.20	1489.23

Therefore, sex effect might be important to include as a fixed effect in our model. Including the sex factor, the mean model becomes

$$y_i = \mu + s_i + x_{i|j}a + e_{i|j} \tag{14}$$

where s_i is the sex effect for individual i. The linear predictor of the dispersion model is therefore $\mu^* + s_i^* + x_{i|j}a^* + e_{i|j}$. QTL and vQTL scan was performed again using DGLM with sex effect (Figure 6).

We see that some peaks vanished in the scan using the model with fixed sex effect. This is mainly because some residual variance in the model without sex effect was explained by the sex effect.

Model Comparison

Table 3 compares the goodness of fit for the models with and without sex effect. The indicator we recorded is the minus logarithm of p-values of the additive genetic effect, so the bigger values indicate the smaller p-values, which namely indicate better fitting of the model.

In Table 3, the p-values become different obviously from the 112th day. That might

Table 3: **Summary of the minus logarithm of p-values of two different models.**

Time Point	-log(p-value) of additive genetic effect			
	Model without Fixed Effect		Model with Fixed Sex Effect	
	Mean model	Disp. Model	Mean model	Disp. model
1st day	6.72	4.31	6.90	4.37
8th day	19.18	6.80	19.32	7.25
46th day	60.69	9.64	72.08	5.16
112th day	50.40	10.68	118.00	8.10
200th day	47.169	6.24	134.20	7.09

be because chicken's sexual maturity is about 16 weeks and growing period is about 18 weeks[1]. The time is just around 112 days. At the end of chicken's growing period and sexual maturity, it shows that the increasing of body weight becomes stable, and the effect of sex becomes significant. Table 2 can be a proof of the time of sexual maturity. One can see that the mean body weights distinguished by sex becomes quite different from the 112th day. Table 4 is an evidence of chicken's growing period, which shows that chickens grow fast between 46 and 112 days, and after 112 days, the increasing of body weight becomes slow.

Table 4: **Growth of the chickens during different time periods.**

Time Period	Average Growth (g)
1-8 days	1.48
8-46 days	7.04
46-112 days	9.23
112-200 days	4.05

[1]http://www.uthsc.edu/compmed/Avian.html

The fixed sex effect should be included in the DGLM for QTL and vQTL scan. Note that the vQTL scan that we performed may not only pick up vQTL but also epistatic QTL when the test loci have certain interaction with other loci (RÖNNEGÅRD and VALDAR 2010).

CONCLUSIONS

We performed both QTL and vQTL detection for a Red Jungle Fowl $\times$ White Leghorn cross using DGLMs. It was shown that DGLM is a proper and efficient approach for localizing variance-controlling QTL. We compared two models with or without fixed sex effect and prefer including the sex effect in order to reduce the residual variances. We found that different genes might take effect on the body weight at different time as the chicken grows.

AUTHORS CONTRIBUTIONS

YH studied the literatures and drafted one part of the paper. LZ implemented the codes in R, analyzed the data, and drafted the other part of the paper. Both authors approved the final version after discussion.

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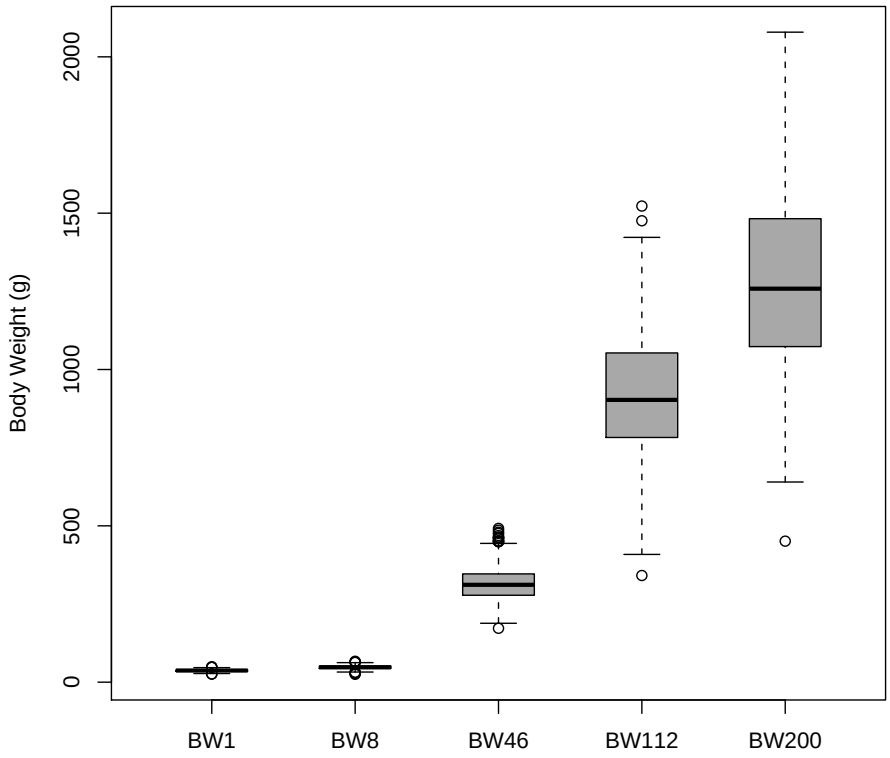

Figure 3: **Boxplots of the body weight records at five time points**. BWt on the horizontal axis indicates the body weight at t days of age.

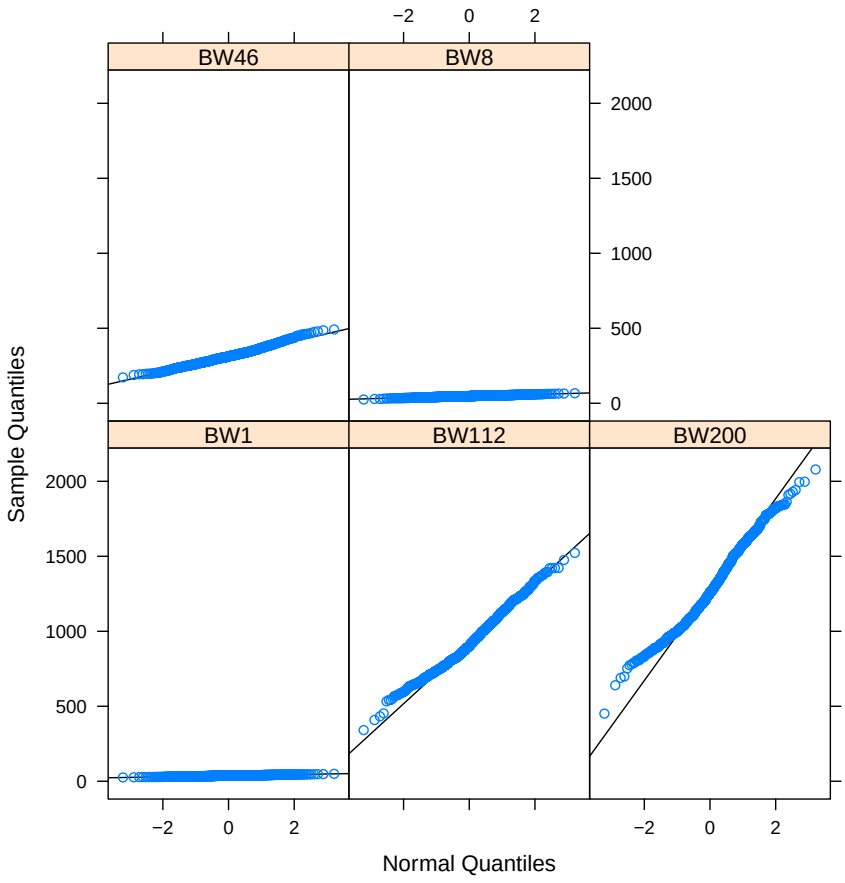

Figure 4: **Q-Q plots of the body weight records at five time points**. BWt on the bars indicates the body weight at t days of age.

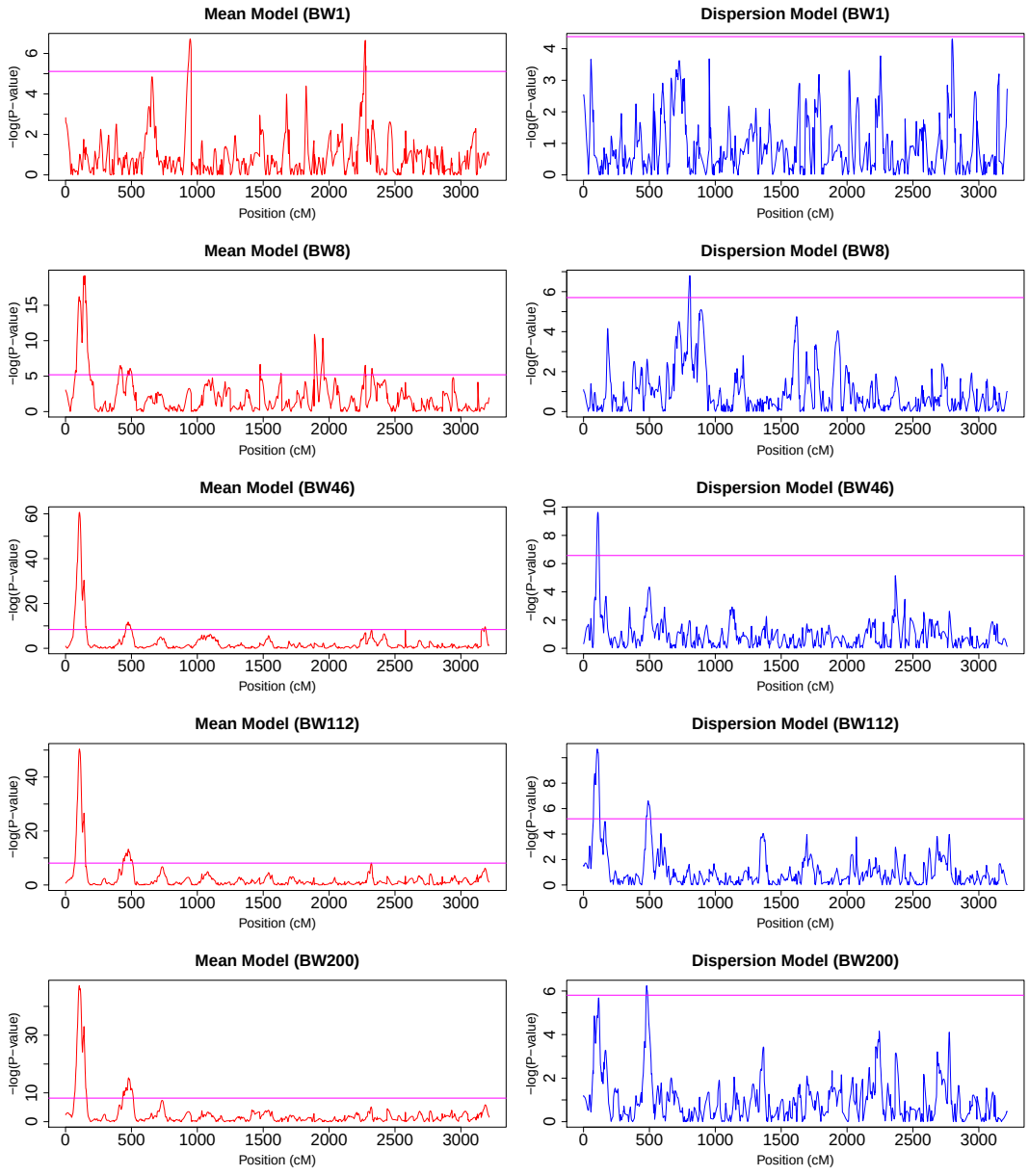

Figure 5: **QTL and vQTL scan for the body weight records at five time points.**. No fixed effect was included in the DGLM. BWt in the title indicates the body weight at t days of age. The horizontal line in each subfigure is the 95% significance threshold.

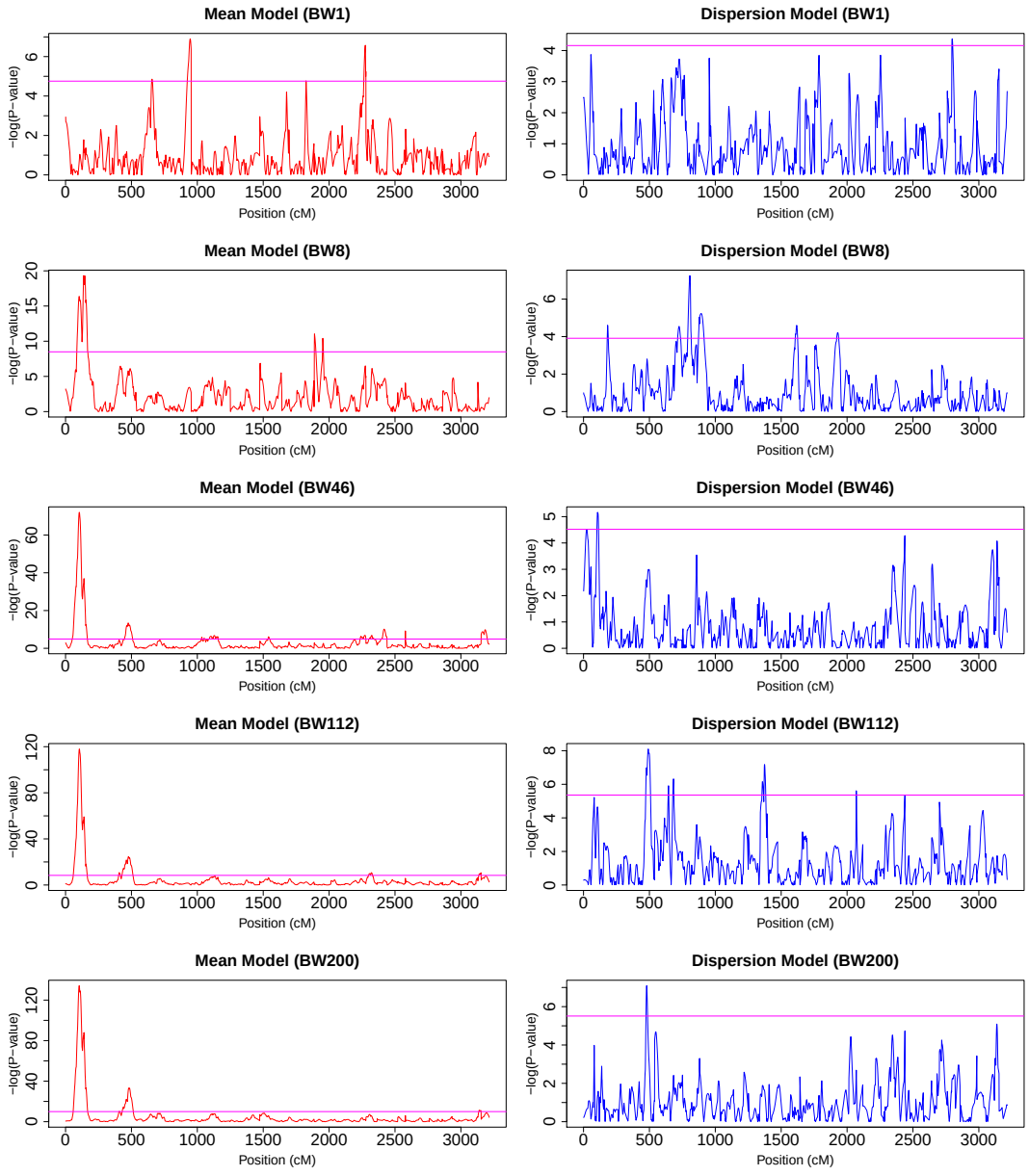

Figure 6: **QTL and vQTL scan for the body weight records at five time points.**. A fixed sex effect was included in the DGLM. BWt in the title indicates the body weight at t days of age. The horizontal line in each subfigure is the 95% significance threshold.