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Araştırma Makalesi

Power of Some Statistical Tests for the Detection of Major Genes in Quantitative Traits: I. Tests of Variance Homogeneity

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Abstract

In this study the power of four within-family variance homogeneity tests (Levene, O'Brien, Brown and Forsythe, and Bartlett test) to detect major genes controlling quantitative traits was evaluated using simulated data. The data were simulated according to a balanced half-sib family structure. One hundred and twenty eight scenario of major gene segregation based on all possible combinations from 4 levels of polygenic heritability (0.2, 0.4, 0.6 and 0.8), 2 modes of inheritance (additive and dominant), 4 levels of gene frequency (0.2, 0.4, 0.6 and 0.8) and 4 levels of major gene effect in phenotypic standard deviation (σ_P=0.5, 1, 2 and 3) were considered. Results showed that the power of all tests advanced with the increase of gene effects. It is observed that the determination of dominant genes was easier than additive ones. The power of all evaluated tests were very poor at the small levels of gene effects (0.5 and 1 σ_P). But the power of tests, particularly in the existence of dominant genes, were dramatically increased when the magnitude of the major gene effect changed from 2 to 3 σ_P. The best power was obtained from Levene and Bartlett tests, respectively. As a conclusion, these simple tests could be used as first indicators of major gene segregation in animal populations.

Key words: Quantitative traits, major gene, detection, statistical tests, simulation

Kantitatif Karakterlere Etkili Major Genlerin Belirlenmesi Bakımından Kimi İstatistiki Testlerin Güçleri: I. Varyans Homojenliği Testleri

Özet

Bu çalışmada, kantitatif karakterlere etkili major genlerin belirlenmesi bakımından dört farklı familya-içi varyans homojenliği testinin güçleri simülasyonla türetilen veriler kullanılarak değerlendirilmiştir. Veriler, dengeli bir üvey-kardeş familya yapısına göre türetilmiştir. Poligenik kalıtım derecesinin 4 düzeyi (0,2, 0,4, 0,6 ve 0,8), iki farklı kalıtım tarzı (kodominant ve dominant), 4 farklı gen frekansı düzeyi (0,2, 0,4, 0,6 ve 0,8) ve 4 farklı gen etkisi düzeyinin (σ_P = 0,5, 1,0, 2,0 ve 3,0) tüm olası kombinasyonuna dayanan toplam 128 farklı major gen açılımı senaryosu değerlendirilmiştir. Sonuçlar gen etkisindeki yükselme ile birlikte tüm testlerin gücünün arttığını göstermiştir. Dominant etkili genlerin belirlenmesinin kodominant etkili genlerden çok daha kolay olduğu gözlemlenmiştir. Gen etkisinin küçük düzeylerinde (0.5 ve 1 σ_P) değerlendirilen tüm testlerin güçleri oldukça zayıf bulunmuştur. Ancak, major genin etkisinin büyüklüğü 2 σ_P'dan 3 σ_P'ya çıktığında testlerin güçleri, özellikle de dominant genlerin varlığında, önemli oranda artmıştır. Değerlendirilen testler içerisinde en yüksek güç sırasıyla Levene ve Bartlett testlerinden elde edilmiştir. Sonuç olarak, bu basit testler hayvan populasyonlarında major genlerin açılımının ilk göstergesi olarak kullanılabilirler.

Anahtar kelimeler: Kantitatif karakterler, major gen, belirleme, istatistiki test, simülasyon

Introduction

The classical animal breeding theory for quantitative traits is based on the polygenic model of inheritance that assumes many genes having small effects on the expression of the phenotype. This theory has been successfully applied in animal and plant breeding. However, during the last two decades, several genes having a major effect on commercial traits have been identified in farm animals. Such loci are referred to as major loci or quantitative trait loci (QTL). The inclusion of major gene information could improve efficiency of selection programs and would develop understanding of the biology of traits. A major gene is defined as the one having an effect of at least one phenotypic standard deviation (σ_P) between two opposite homozygotes (Roberts and Smith, 1982). Despite this definition, with the advances of molecular genetics and statistical methods in the last years, detection of major genes with smaller effect has been possible. However, detection of major genes without genetic marker information will remain

important due to some difficulties in molecular applications (Elsen and Le Roy, 1995).

Notable examples for major genes are the Booroola and Inverdale genes affecting ovulation rate (Piper and Bindon, 1982; Davis et al., 1988) and the callipyge gene affecting meat production in sheep (Cockett et al., 1993), the double muscling gene affecting meat production in cattle (Hanset and Michaux, 1985a,b), the halothane sensitivity and the RN gene affecting meat quality (Archibald and Imlah, 1985), the estrogen receptor locus affecting litter size in pigs (Rothschild et al., 1996), and the naked neck gene affecting heat tolerance and dwarf gene affecting body size in poultry (Merat, 1990).

When a major gene, whose effect is large enough, segregates in population there will be heterogeneity of the variance within-families, because the major gene will be segregating in some sire families but not in others as a result of parent genotype (Le Roy and Elsen, 1992; Falconer and Mackay, 1996). Many authors indicated the possibility of applying the tests of within-family variance homogeneity (Elsen and Le Roy, 1990; Le Roy and Elsen, 1992; Falconer and Mackay, 1996; Lynch and Walsh, 1997) for the detection of major genes. But, more detailed properties of within-family variance homogeneity tests except Bartlett (Le Roy and Elsen, 1992) for the detection of major genes were not studied until now. From this point of view, the present paper aimed to evaluate power of a number of within-family variance homogeneity tests for the detection of these genes.

Materials and Methods

Experimental Design

The power of within-family variance homogeneity tests for the identification of major genes were evaluated by the comparison of polygenic and mixed (polygenes + a major gene) inheritance models. The polygenic data were simulated according to a balanced half-sib family structure: each data set consists of 50 sire families with 20 dams per sire and one progeny per dam. Sires and dams are assumed to be unrelated and one phenotypic observation was simulated for each progeny. The model to describe the data based on polygenic inheritance can be represented as:

$$y_{ij} = \mu + s_i + e_{ij}$$

where y_{ij} is the observation of jth progeny of ith sire, μ is the overall population mean of the polygenic and environmental components (set to zero), s_i is the random effect of ith sire (i.e. polygenic component) and $e_{ij}$is the residual random effect for each progeny.

The true breeding values of progenies were obtained from a normal distribution with mean zero and variance $\sigma_a^2 = (¼\, h^2)\sigma_P^2$ where phenotypic variance (σ_P^2) was set equal to 1. Their residual values were generated from a normal distribution with mean zero and variance $\sigma_e^2 = (1 - ¼\, h^2)\sigma_P^2$. Then the phenotypic value for each progeny was obtained as the sum of the true breeding value (~N(0, σ_a^2)) and the residual value (~N(0, σ_e^2)) where N represents the normal distribution. By this way, for different values of polygenic heritability (h^2= 0.2, 0.4, 0.6 and 0.8), 4 separate data sets each contain 100 replicates were simulated.

A single major gene with two alleles (*A* and *a*) was considered. There are three genotypes, *AA*, *Aa*, and *aa*, taking genetic value as *a*, *d*, and *–a*, respectively, where *a* is the additive and *d* is the dominant genetic effect. The effect of major gene in phenotypic standard deviation (σ_P) unit was considered as the difference of two homozygotes ($2a=\mu_{AA}-\mu_{aa}$). The dominance of the major gene was defined by $d=\mu_{Aa}-(\mu_{AA}+\mu_{aa})/2$. The parameter set up used for all tests was as the following: polygenic heritability ($h^2 = 4\sigma_a^2 / \sigma_P^2$) took values of 0.2, 0.4, 0.6, or 0.8; type of dominance took values of d=0 (additive or codominant), or d=a (complete dominance); frequency of the major gene p*(A)* took values of 0.2, 0.4, 0.6, or 0.8; and magnitude of major gene effect as difference of two homozygotes in σ_P unit took values of 0.5, 1, 2, or 3. Thus, 128 scenario of major gene segregation based on all possible combinations from 4 levels of polygenic heritability, 2 modes of inheritance, 4 levels of gene frequency and 4 levels of major gene effect were examined with various test statistics.

For parents, the genotypes of the major gene were calculated from given allele frequency. Then the genotype of progenies assigned from their parent's genotypes. Major gene effects were added to polygenic data of progenies according to their genotypes using uniform random numbers. Consequently, polygenic effects and major gene effect was combined in the following statistical model to obtain mixed (polygenes + a major gene) data:

$$y_{ij}^k = \mu_k + s_i + e_{ij}$$

where y_{ij}^k is the observation of jth progeny of ith sire with major genotype k (*AA, Aa* and *aa*), μ_k is the mean

value of the performances of genotype *k* progeny, s_i is the random effect of i[th] sire (i.e. polygenic component) and $e_{ij}$is the residual random effect.

Let H_0 and H_1 be the hypotheses of polygenic and mixed (polygenes + a major gene) inheritance, respectively. Under H_0 we consider within-family variances are homogeneous as a result of polygenic inheritance. For each of the test statistics, power represents probability of rejecting the null hypothesis when the alternative hypothesis is true. The power of investigated tests at the 5% error level was estimated for each situation studied by taking the number of test statistic values that exceeded the corresponding H_0 quantile. The power of all tests was estimated from 100 replications. The robustness of the test statistics was not examined.

Statistical tests and analyses

For the simulation of data sets and statistical analyses a macro was written in SAS Macro Language and all simulations and analyses were performed by SAS software (SAS, 1999a,b). For the investigation of power of the within-family variance homogeneity tests to detect major genes, Levene (L), O'Brien (O'B), Brown and Forsythe (B-F), and Bartlett (B) tests (Levene, 1960; Brown and Forsythe, 1974; O'Brien, 1979; Le Roy, 1989) were compared. These tests except Bartlett test were not evaluated for this purposes until now.

These tests except Bartlett is transform the original values of the dependent variable to derive a dispersion variable and then analysis of variance are performed on this variable. Afterwards the major gene hypothesis (H_1) is accepted when the F test of the model is significant. Details of evaluated tests are given as follows:

Levene's test (L)

Levene's test (Levene, 1960) is widely considered to be a standard test for homogeneity of variance. This method is based on the analysis of variance of dispersion variables, Z_{ij}^{L}, estimated as squared difference between any observation and its group means:

$$Z_{ij}^{L} = (y_{ij} - \bar{y}_{i.})^2$$

where y_{ij} is the performance of j[th] progeny of i[th] sire and $\bar{y}_{i.}$ is the mean of i[th] sire group.

O'Brien's test (O'B)

O'Brien (1979) suggested a test that is basically a modification of Levene's dispersion variable (Z_{ij}^{L}), using the following dispersion variable:

$$Z_{ij}^{W} = \frac{(\mathrm{W} + n_i - 2)(y_{ij} - \bar{y}_{i.})^2 - \mathrm{W}(n_i - 1)\sigma_i^2}{(n_i - 1)(n_i - 2)}$$

where W is a rarely critical value that can be used to tune O'Brien's Z_{ij}^{W} dispersion variable to match the suspected kurtosis of the underlying distribution, n_i is the size of i[th] sire group and σ_i^2 is its sample variance.

As in the Levene's test, an analysis of variance applied to O'Brien's dispersion variable.

Brown and Forsythe test (B-F)

Brown and Forsythe (1974) suggested a test for homogeneity of variance based on analysis of variance using the dispersion variable obtained from the absolute deviations from the group medians. The dispersion variable estimated as:

$$Z_{ij}^{BF} = | y_{ij} - m_i |$$

where m_i is the median of i[th] sire group.

Bartlett's test (B)

The use of Bartlett test for the detection of major genes is suggested elsewhere (Merat, 1968; Hanset and Michaux, 1985b). The power of this test has studied by Le Roy and Elsen (1992) for livestock populations. Bartlett's test is a χ^2 test of within group homogeneity of variances (Le Roy, 1989; Yıldız et al., 1998). It is based on the following statistics:

$$\chi^2 = \frac{2.303}{\mathrm{c}}\left[(\mathrm{n}-\mathrm{t})\log\tilde{\mathrm{s}}^2 - \sum_{\mathrm{i}=1}^{\mathrm{t}}(\mathrm{n}_\mathrm{i}-1)\log\hat{\mathrm{s}}_\mathrm{i}^2\right] \sim \chi^2_{\alpha,\,\mathrm{t}-1}$$

where

$$\mathrm{c} = 1 + \frac{1}{3(\mathrm{t}-1)}\left(\sum_{\mathrm{i}=1}^{\mathrm{t}}\frac{1}{\mathrm{n}_\mathrm{i}-1} - \frac{1}{\mathrm{n}-\mathrm{t}}\right) \text{ and}$$

n_i is the size of i[th] family, n is the total number of individuals, t is the number of families, $\hat{s}_i^2$ is the variance of i[th] family and $\tilde{s}^2$ is the general variance.

Results

Simulation results on the power of within-family variance homogeneity tests for detection of major genes were given under separate headings according to mode of major gene inheritance (additive and dominant).

Power of the tests for detection of additive major genes

The power (%) of within-family variance homogeneity tests for the detection of additive major genes with 0.5,

1, 2 and 3 σ_P of gene effect are given in Table 1. These results showed that the power of all tests increased with the gradual increase of gene effect from 0.5 to 3 σ_P. The level of polygenic heritability does not have an obvious effect on the power of tests for the detection of additive major genes.

The performances of all tests were quite low (maximum 4%) for the detection of additive major genes with $0.5\sigma_P$ of gene effect. The power of within-family variance homogeneity tests were not affected by the different frequencies of major genes at this level.

The power of tests increased a little bit with the increase of gene effect to 1 σ_P and were not affected by different frequencies of major genes. The Levene's test was powerful than other within-family variance homogeneity tests.

All tests' power was significantly increased (maximum 18%) when effect of major gene increased to $2\sigma_P$. In this level of gene effect the Levene test is more powerful than other tests. There is no clear association between the power of tests and frequency of major gene.

When the additive major gene have a gene effect of $3\sigma_P$, power of all tests were increased. The power of all within-family variance homogeneity tests, especially of Brown and Forsythe, and Bartlett tests, were higher for extreme gene frequencies (p=0.2 or 0.8) than intermediate (p=0.4 or 0.6). The Levene and O'Brien tests were rather powerful than Brown and Forsythe, and Bartlett tests.

Power of the tests for detection of completely dominant major genes

The power (%) of within-family variance homogeneity tests for the detection of dominant genes with 0.5, 1, 2 and $3\sigma_P$ of major gene effects are presented in Table 1. As in the case of additive major gene segregation, power of the all studied tests for detection of dominant major genes were not affected by level of polygenic heritability. Similarly, the power of all tests increased with the increase of gene effect from 0.5 to $3\sigma_P$. The performances of all tests were very low for the detection of major genes with 0.5 and 1 σ_P of gene effect. The power of tests was increased suddenly for a gene effect of 2 or $3\sigma_P$.

The power of all tests was fairly low for the detection of major genes with $0.5\sigma_P$ of gene effect. Only the Levene test was reached to a power of 6% in a few situations. But, the power of all of other tests was smaller than or equal to 3%. The power of the tests were not changed with the increase of frequency of major genes.

With the augmentation of major gene effect from 0.5 to $1\sigma_P$ the power of all tests partially increased (maximum 14%).

Table 1. The power (%) of the within-family variance homogeneity tests for the detection of additive major genes with different level of gene effect (0.5 to 3.0 σ_P).

Polygenic h^2	Major gene frequency	0.5 σ_P				1.0 σ_P				2.0 σ_P				3.0 σ_P			
		L	O'B	B-F	B	L	O'B	B-F	B	L	O'B	B-F	B	L	O'B	B-F	B
0.20	0.2	3	0	0	1	2	1	0	2	18	8	3	7	27	21	6	12
	0.4	3	1	1	2	3	1	0	1	18	11	3	7	23	16	3	6
	0.6	1	1	0	0	4	0	0	2	9	6	1	1	26	16	5	6
	0.8	4	1	0	0	3	1	0	1	14	8	1	4	27	20	7	8
0.40	0.2	1	0	0	0	3	2	1	3	13	10	3	9	30	20	6	14
	0.4	3	2	0	1	3	1	1	4	13	9	3	6	24	18	3	7
	0.6	2	0	0	1	3	0	1	1	15	6	4	5	25	14	1	2
	0.8	3	0	0	1	3	1	0	0	9	4	1	6	26	17	10	15
0.60	0.2	0	0	0	0	2	1	0	0	8	4	3	7	25	15	9	19
	0.4	0	0	0	0	1	0	1	0	12	8	1	6	33	19	6	4
	0.6	2	1	0	0	4	1	0	1	10	2	0	4	15	9	3	2
	0.8	0	0	0	0	2	1	1	1	11	9	4	9	32	23	9	18
0.80	0.2	0	0	0	1	1	0	0	1	15	9	1	7	28	19	9	18
	0.4	0	0	0	0	2	0	0	1	6	3	3	3	24	16	3	6
	0.6	0	0	0	0	1	1	1	1	7	6	4	3	22	11	2	3
	0.8	0	0	0	0	1	0	1	1	11	4	1	5	29	20	10	18

Abbreviations: h^2: heritability, σ_P: phenotypic standart deviation, L: Levene, O'B: O'Brien, B-F: Brown and Forsythe, B: Bartlett

Table 2. The power (%) of the within-family variance homogeneity tests for the detection of dominant major genes with different level of gene effect (0.5 to 3.0 σ_P).

Polygenic h^2	Major gene frequency	0.5 σ_P				1.0 σ_P				2.0 σ_P				3.0 σ_P			
		L	O'B	B-F	B	L	O'B	B-F	B	L	O'B	B-F	B	L	O'B	B-F	B
0.20	0.2	4	0	0	2	4	0	0	3	6	4	1	3	17	6	8	3
	0.4	2	2	1	1	8	1	0	2	58	48	25	37	100	100	96	99
	0.6	4	0	0	1	8	4	0	0	81	73	52	83	100	100	100	100
	0.8	3	1	0	0	5	2	0	2	23	12	2	30	65	56	20	98
0.40	0.2	1	0	0	1	3	3	2	3	11	3	1	1	15	8	7	9
	0.4	1	1	0	0	8	3	2	4	59	39	33	40	100	100	98	100
	0.6	6	1	0	3	9	4	0	6	87	77	63	91	100	100	100	100
	0.8	4	0	0	0	5	0	0	2	22	17	2	38	66	59	15	99
0.60	0.2	0	0	0	0	4	2	1	2	12	6	2	4	11	7	8	6
	0.4	2	0	0	0	10	5	5	7	74	61	43	54	100	100	98	100
	0.6	1	0	0	0	7	6	2	5	82	79	60	88	100	100	100	100
	0.8	1	0	1	0	3	1	0	1	19	15	2	31	80	67	21	100
0.80	0.2	2	1	0	0	5	3	1	4	15	9	5	7	20	10	11	10
	0.4	0	0	0	1	14	8	3	5	73	60	47	52	100	100	99	100
	0.6	1	0	0	0	3	1	0	4	96	93	80	96	100	100	100	100
	0.8	0	0	0	1	4	2	2	2	26	19	3	50	82	73	15	99

Abbreviations: h^2: heritability, σ_P: phenotypic standart deviation, L: Levene, O'B: O'Brien, B-F: Brown and Forsythe, B: Bartlett

Within-family variance homogeneity tests were more powerful in moderate gene frequencies, especially in the major gene frequency of 0.4. The Levene's test is more powerful within-family variance homogeneity test at this level.

A sharp increase in the power of tests were observed when the magnitude of segregating dominant major gene effect increased from 1 to $2\sigma_P$. In most situations, in particularly at major gene frequencies of 0.2 and 0.6, power of tests was over 50%. Furthermore, the power of tests was over the 80% in some cases. Within-family variance homogeneity tests appear more powerful when the frequencies of major gene are intermediate (p=0.4 or 0.6). On the other hand, power of these tests was rather low in extreme frequencies (p=0.2 or 0.8). According to their power within-family variance homogeneity test may be ranked as Levene, Bartlett, O'Brien, and Brown and Forsythe, respectively, at this level of gene effect.

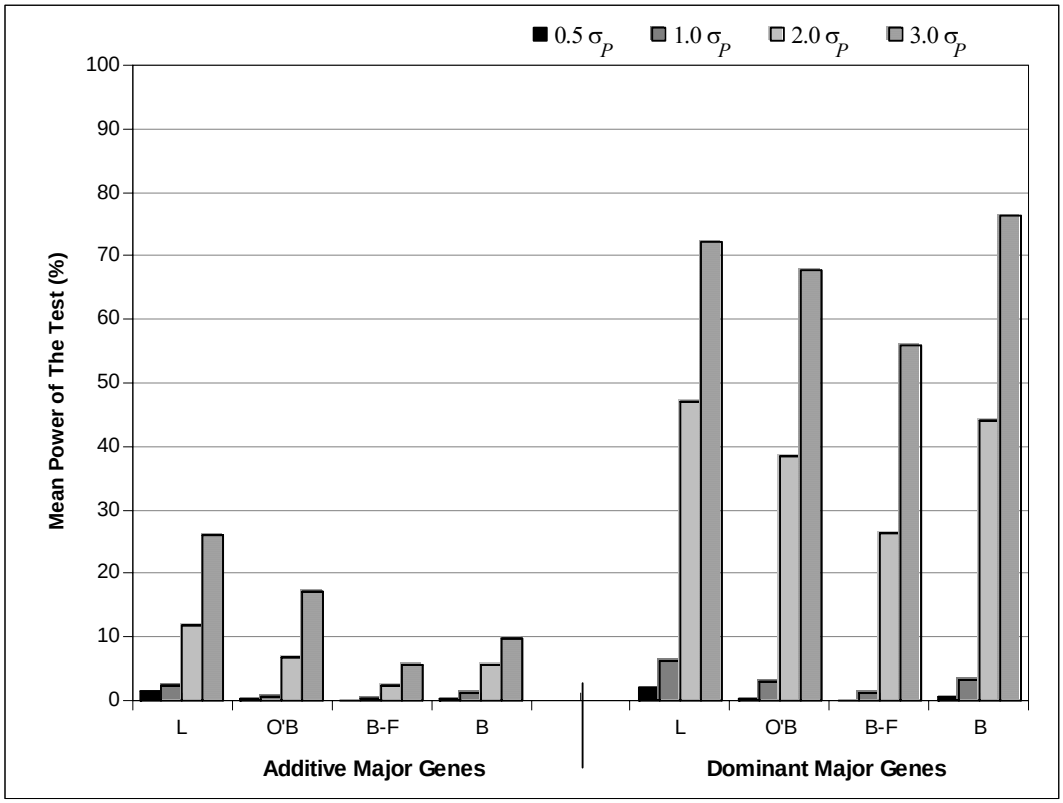
In most situation of the existence of dominant major genes with an effect of $3\sigma_P$, the power of the tests, in particularly at intermadiate gene frequencies, reached to approximately 100%. In this case, Bartlett is superior test. The power of all tests were rather low when the major gene frequency is 0.2. Similarly, power of the all tests except Bartlett were some lower at the gene frequency of 0.8.

Mean power of the tests

To clarify the results, power of the tests at the 4 level of gene frequency and 4 level of polygenic heritability were joined in one mean to obtain average power of the each test. Mean power of the within-family variance homogeneity tests for the detection of additive and dominant major genes with different level of gene effects (0.5 to 3 σ) are given in Figure 1.

The power of variance homogeneity tests was rather low in all cases of additive gene action and the mean power of all tests was smaller than 26%. With a gene effect of $\leq 2\sigma_P$, none of variance homogeneity tests had an average power greater than about 12%. The power of Levene's test is superior to other within-family variance homogeneity tests when an additively inherited major gene segregates in population.

In the existence of dominant genes, the mean power of all of the within-family variance homogeneity tests except Brown and Forsythe was over the 50% for a $3\sigma_P$ of major gene effect. With a gene effect of $2\sigma_P$, the mean power of within-family variance homogeneity tests varied between 26-47%. The power of Bartlett's variance homogeneity test is better than Levene's test. This is contrasted with the case of additive major gene segregation. Power of the tests were rather low at the gene effect of 0.5 or 1.0 σ_P.



Abbreviations: σ_P : phenotypic standard deviation, L: Levene, O'B: O'Brien, B-F: Brown and Forsythe, B: Bartlett

Figure 1. Mean power (%) of the within-family variance homogeneity tests for the detection of additive and dominant major genes with different level of gene effects (0.5 to 3 σ_P).

Discussion

The dominant major genes were determined more easily than additive ones in all scenarios of major gene segregation. Same results were reported in other studies (Le Roy, 1989; Knott and Haley, 1991; Janss and Van Der Werf, 1992; Le Roy and Elsen, 1992; Elsen and Le Roy, 1995). When an additive major gene is segregating, all tests are powerful for extreme gene frequencies (0.2 or 0.8) than moderate (0.4 or 0.6). In contrast, the power of within-family variance homogeneity tests is superior for moderate gene frequencies when a dominant gene exists.

Up to date, as within-family variance homogeneity test, only the Bartlett test was used on actual data by Le Roy (1989) and Ricordeau et al. (1989) and existence of major genes was supported in these studies.

Detection of major genes is a more important issue today. The simple statistical methods evaluated in this study could be used in a systematic way as first indicators of major gene segregation in animal populations. Segregation of additive major genes with 3 or more and of dominant major genes with 2 or more σ_P of gene effect may be easily determined by these simple tests. Checking data with more than one test of within-family variance homogeneity may be more meaningful due to different power of tests to various situations of major gene segregation. Concerning the power, the use of Levene and Bartlett within-family variance homogeneity tests are primarily recommended. However, if environmental variation is sufficiently high relative to the effects of any individual gene or if major alleles are at low frequency, the effects of segregating major genes can be entirely obscured. Therefore, the effects of macro environmental components need to be removed from phenotypic data to make these tests more powerful. When positive results obtained for any major genes based on these simple tests, these results would have to be confirmed and detailed by

more complicated methods such as segregation analysis of phenotypic data or molecular genetic methods.

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