academicJournals

Vol. 9(17), pp. 758-767, 15 September, 2014
DOI: 10.5897/SRE07.099
Article Number: F0B3C9047290
ISSN 1992-2248 © 2014

http://www.academicjournals.org/SRE

Scientific Research and Essays

Full Length Research Paper

Applying robust variance components models in the analyses of major gene effects within fragile X families

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Received 13 June, 2007; Accepted 11 February, 2011

The effect of the fragile X allele on ridge breadth, height and testicular volume was examined using robust statistical techniques for the data collected from 8 families from Ibadan, south west Nigeria, afflicted with this disorder. There is the presence of outliers, an estimated 6.5% for testicular volume and 1.3% for ridge breadth and height data respectively. It is shown that fragile X affects ridge breadth, height and testicular volume in a different manner. Fragile X women had a greater mean ridge breadth than normal women; a pattern similar to normal and fragile X men but the differences were not significant. Fragile X men were shorter than normal men, but no significant difference between the mean height of normal and fragile X women was observed. Whereas fragile X girls were shown to grow more quickly and to stop growth earlier than normal girls, normal women were taller than fragile X women. Testicular volume in fragile X boys continue in development long after normal boys have stopped; an observation that could explain the significant difference in means of adult males. An examination of the covariance between relatives classified according to fragile X status showed that for the three traits the influence of fragile X alleles was to reduce the covariance between parents and offspring, the effect of which produces a departure from an additive polygenic model of inheritance.

Key words: Fragile X allele, ridge breadth, testicular volume, single-gene disorder.

INTRODUCTION

Of one of the most frequent single-gene disorders recognised in humans, the fragile X is of particular interest and concern because it is one of the most frequent and it represents a wide spectrum of clinical manifestations including intellectual capability and physical defects (Garber et al., 2008; Kabakus et al., 2006). The molecular basis of fragile X has the form of an unstable CGG repeat within the “fragile X mental retardation” (FMR1) gene (Glover-Lopez and Guillen-Navarro, 2006; Verkerk et al., 1991). The expansion of this repeat beyond a particular threshold causes transcriptional suppression. The instability of the CGG repeat combined with other features of the fragile X genotype (Terracciano et al., 2005; Heitz, et al., 1992; Warren and Nelson, 1994) complicates the genotype-phenotype relationship in this condition. Extensive variability of clinical expressions between different families and particularly between different generations within a family could be observed because of the phenomenon of anticipation, that gradual deterioration of clinical status (Korneluk and Narang, 1997; Van Esch et al., 2005). If the effect of the unstable fragile X mutation on a quantitative trait is considered, simple descriptive procedures such as scatter plots, typically reveal a

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number of outliers. The analysis of such data requires a methodology which is specifically tailored to handle data where data exist with extensively varying observations are the rule rather than the exception (Huggins and Loesch, 1995).

Concerning genetic and non-genetic effects on quantitative traits, there had been various hypotheses concerning testing a trait using maximum likelihood techniques under the assumption of multivariate normality. However, despite the fact that (Lange, 1978) has given theoretical justification of the assumption of multivariate normality for polygenic traits, it is relatively common that this assumption is violated (Huggins, 1993).

Huggins (1993) has developed a robustified likelihood procedure which supposes that the bulk of the data is multivariate normal with a proportion of contamination due to outliers, and that the analysis is only interested in modelling the central multivariate portion of the data. This differs from the procedures employed by other authors such as (White, 1982; Beaty, 1985; Royall, 1986) and those who obtained estimates which are robust against model misspecification, of the variance of the maximum likelihood estimates computed under the assumption of multivariate normality.

In the past, standard maximum likelihood methods were largely used to analyse data on some physical and intellectual measures in human pedigrees affected with fragile X (Loesch et al., 1992; Loesch et al., 1993).

Robust statistical methodology have previously been used by Huggins (1993) to derive a test for the detection of major gene effects in the presence of the fragile X mutation in the highly heritable polygenic trait, ridge count. A similar application on ridge breadth and height was also reported in Huggins and Loesch (1995). Here the use of pedigree data and the highly sophisticated statistical analysis was employed to eliminate the effect of the fragile X mutation on the means and variance components of height, ridge breadth and testicular volume in which averages of the ridge breadth and the testicular volumes were taken on the left and the right hands for ridge breadth, and bilaterally for testicular volume respectively. This approach fits models to the central multivariate central portion of the data and precludes the use of subjective screening procedures to determine if there is an atypical observation to be removed from the data sets.

These traits were chosen for the following reasons. Firstly, they were found to be affected in adult fragile X individuals by simple group comparisons (Loesch 1986; Loesch et al., 1988). Therefore, they can conveniently be used in the application of robustified likelihood procedures for the analysis of quantitative traits which are normally determined by a larger number of additive genes but which in abnormal conditions are modified by the effect of a gene mutation. Moreover the result of the analysis are of interest to biologists and clinicians as they contribute to a better understanding of the extent and of the pathomechanisms of growth abnormalities in fragile X.

MATERIALS AND METHODS

The data

Data was collated from a previous study on 8 African Negroid families living in south western Nigeria (Latunji, 2008). Data on two antropometric and one dermatoglyphic phenotypic traits for fragile X individuals and their participating relatives. Ridge breadth was estimated between two palmer interdigital triradii, a and b, by dividing the distance between these triradii by the number of ridges between them plus 1, as described in Huggins and Loesch' (1995)

Length (l) and width (w) of the testis was measured with a caliper and the volume (V) was calculated according to the formular $V= w^2l\pi/6$ (Mingroni-Netto et al., 1990). The average volume of the two testis per individual was taken.

A total of 78 individuals (31 males and 47 females) aged 8 to 78 years, participated in the study (Table 1). Measurements on ridge breadth and height were available from all while the males supplied the data on testicular volume. The composition of the data set by sex and fragile X status is given in Table 2. The number of individuals per pedigree upon which observations on height and ridge breadth is available ranged from 7 to 13 with an average of 9.75. The number per pedigree upon which observations on testicular volume is available ranged from 2 to 8 with an average of 3.88. The average number of generations per pedigree upon which observations on the three traits are available was 2.5.

Scatter plots of the values of ridge breadth in relation to palm width, height to age and testicular volume to age are given in Figures 1, 2 and 3 respectively.

Statistical methods

Robust estimates were computed according to (Huggins, 1993) who gave a similar modification of a log-likelihood which down weights outliers. Residuals were computed according to the methods of (Hopper and Mathews, 1982) but using robust rather than maximum likelihood estimates. If residuals larger than 2.3 are regarded as extreme outliers (that is, observations which are more than 2.3 standard deviations from their expected values) it is was then estimated that there were 1.3% extreme outliers in the ridge breadth data, 1.3% for height and 6.5% extreme outliers for testicular volume. The choice of 2.3 as the threshold for screening extreme outliers is somewhat arbitrary and perhaps conservative. However, it is pertinent for descriptive purposes, as under the multivariate normal model there is a probability of only 0.006 that any particular residual exceeds this amount. In particular under the multivariate normal model, the probability that 1.6% of the residuals in the height and ridge breadth data exceed 2.3 in absolute value is extremely small (0.003), and testicular volume data where 6.5% of these extreme outliers were observed respectively, the probability is far smaller.

Modelling the means

Means were modelled according to Loesch and Huggins (1995). This was based on the clear evidence that ridge breadth is linearly related to palm width in boys and girls but not in adults as observed from scatter plots. Motivated by these plots the model for mean ridge breadth (ridge breadth) was in the form of a regression on palm width for individuals less than 19 years old, and a mean for individuals aged greater than 19 years.

Table 1. Anthropocentric and dermatoglyphic data from the 8 pedigrees.

Pedigrees	Individuals	Palm width	Ridge	Age	Height volume	Testicular breadth
	I – I	7.7	525	38	1590.8	
	I – I*	9.6	580	61	1601.1	27.7
	II - I	7.4	473.1	37	1720	
	II – II*	7.3	495.1	35	1566.1	
	II – III*	8	540.1	48	1690	32.5
A	II – IV	7.2	490	42	1750.8	
	II – V*	9	505.1	40	1791.2	19.4
	II – VI*	5.8	473	13	1355	
	III – I**	7.8	550	17	1670	24.5
	III – II	5.9	518.1	15	1535	
	III – III*	5.5	531.3	12	1355.9	
	I – I*	8	530	61	1520	
	II – I*	9.4	550	39	1840	24.6
	II – II	7.4	475.5	30	1611	
	II – III	7.3	465	28	1551	
	II – IV	7.5	460.5	26	1423	
B	II – V	7.2	550.6	41	1453.7	
	II – VI*	6.2	500.4	51	1710.6	23.8
	III – I*	6.6	490.3	10	1290	15.9
	III – II**	5.6	520.9	13	1390.8	
	III – III	7	490.1	15	1500.9	26.3
	III – IV	6.9	510	18	1580	25
	I – I	7.6	528	46	1550	
	I – II	8.9	682.9	53	1610	25.9
	II – I	7.7	620.2	13	1416.1	
C	II – II**	7.4	513	15	1410.5	26.3
	II – III*	7.1	640.1	16	1485.2	
	II – IV*	7.7	594	16	1510.1	
	II – V	8.5	601.7	22	1473	
	I – I	7.7	498	58	1553.2	
	I – II	7.7	650.1	57	1600	25.4
	I – III	7.3	620.1	41	1580.1	
	I – IV*	6.8	560.6	51	1694	
D	II – I	5.6	420	24	1583	
	II – II*	7.6	575	20	1690.6	20.6
	II – III**	7.9	520	17	1650	28.1
	II – IV	8.2	575	21	1444	
	II – V*	6.7	500	12	1310.1	15.1
	I – I	7.7	540.1	54	1722.4	
	I – II	8.6	690	68	1598	27.6
E	I – III	8.4	475	29	1785.2	33.4
	II – I	7.9	450.5	26	1650.3	24.1
	II – II	7.5	605	48	1610.4	
	II – III*	9.3	680	55	1603.2	22.8
F	II – IV	8.5	575.3	20	1690	25.3
	II – V	7.9	510.8	16	1550.7	25.9

Table 1. Contd.

	II – VI	5.7	414.9	15	1555.1	
	III – I	6.6	665.5	14	1590.5	
	III – II	7.7	525.8	22	1551.1	
	III – III	8.2	560.3	18	1640	23.8
	III – IV**	7.4	571.2	26	1550.6	36.3
	I – I	8.6	622.8	60	1550.7	
	I – II	8.7	620.7	73	1753	25.3
	I – III	7.5	490.3	56	1555.2	
G	I - IV	7.8	520.1	62	1460.2	
	II – I**	8.7	582	30	1580.8	
	II – II	6.1	600.7	17	1550	
	II – III	6.8	590	14	1380.8	
	I – I	7.3	570.3	50	1521	
	I – II	8.8	610.9	58	1699	22.7
	II – I	6.5	503.1	8	1220.6	13.7
	II – II**	8.5	536.4	26	1595	
H	II – III	8	612.2	16	1475.4	
	II – IV	8.1	510.1	20	1473	
	II – V	6	625.6	44	1690.1	24.1
	II – VI	6.9	509.4	29	1561.4	
	II – VII	6.9	510	13	1551	16
	II – VIII	8.1	468	23	1765	
	I – I	6.6	490	32	1601	
	II – I	7.1	690	40	1691	
	II – II	9.4	660.6	44	1790	20.5
	II – III	7.2	495.5	30	1693.1	
I	II – IV	5.7	625	12	1355.3	
	II – V	7.1	610.4	16	1603.1	
	II – VI	7.8	506.6	18	1565.3	30.1
	III – I	6.2	625	18	1601.1	
	III – II	5.4	600.5	14	1370.9	
	III – III**	7.8	618	20	1650.2	

*Normal fragile X allele bearers; **Propositus.

Table 2. Composition of ridge breadth sample and height sample by sex and fragile X status.

Parameter	Normal	Fragile X	Total
Ridge Breadth			
Male	15	16	31
Female	17	30	47
Total	32	46	78
Height			
Male	15	16	31
Female	17	30	47
Total	32	46	78
Testicular volume			
Male	15	16	31

$\mu_{ridge\ breadth} = \{\square^{\mu adults'}/\alpha_{children} + \beta_{children}$ x palm width.

If age ≥=19 otherwise.

The parameters in this model were allowed to vary according to sex and fragile X status.

Modelling for height, the regression models are described as follows: $\mu_{height} = \{\square^{\mu adults'}/\mu_{children} + \theta$ age if age is greater than θ, otherwise, where again the parameters were allowed to vary with sex and fragile X status. It should be noted that in this model the parameter θ represents the age at which growth ends.

Modelling for testicular volume, the regression models are as follows: $\mu_{testicular\ volume} = \{\square^{\mu adults'}/\mu_{children} + \theta$ age) if age is greater than θ, otherwise, where again the parameters were allowed to vary with age and fragile X status.

Modelling the covariance

Two approaches were considered in modelling the covariance

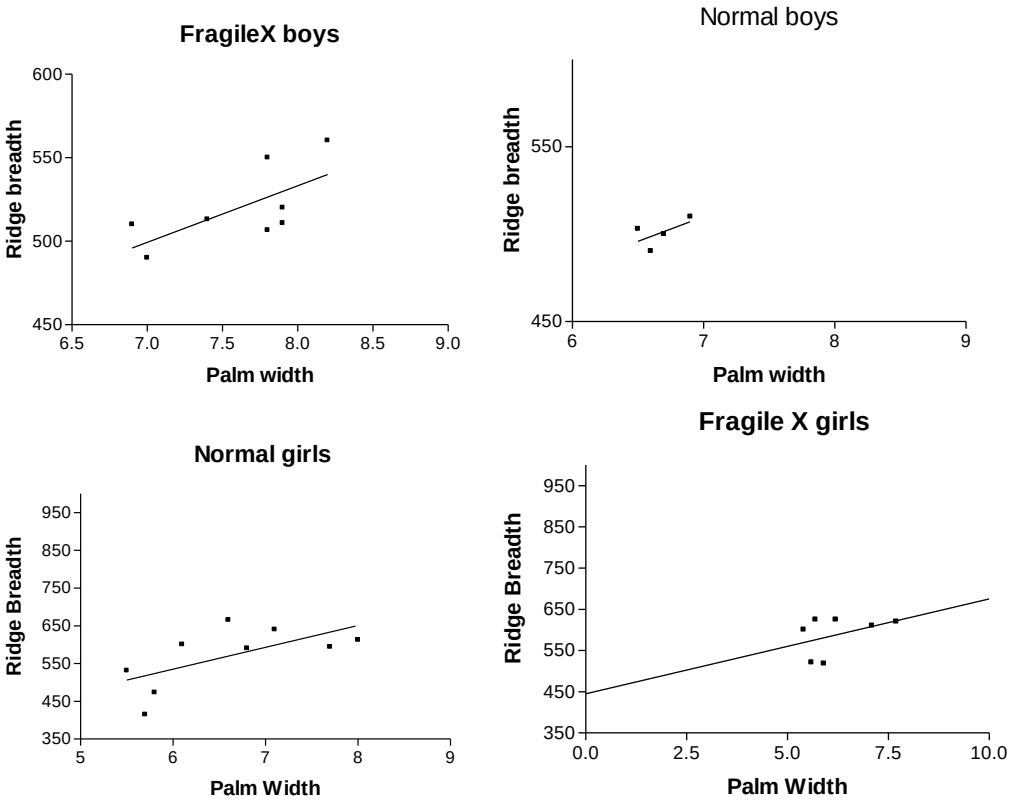

Figure 1. Scatter plots of ridge breadth against palm width in boys and girls.

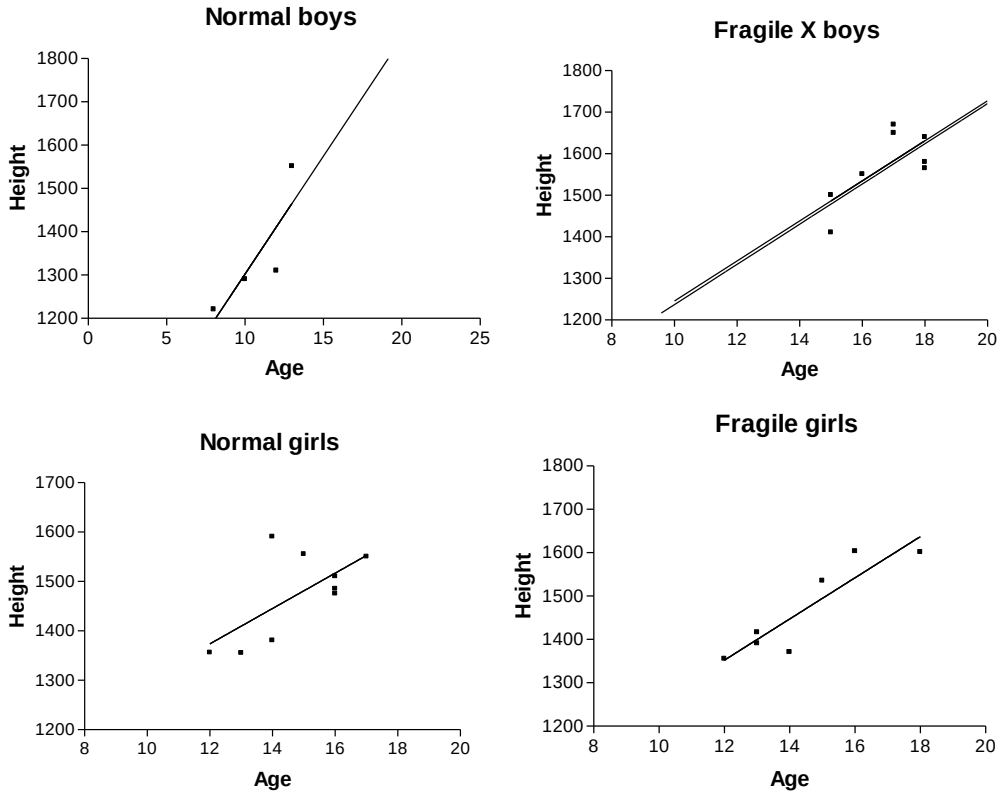

Figure 2. Scatter plots of height (mm) against age in boys and girls.

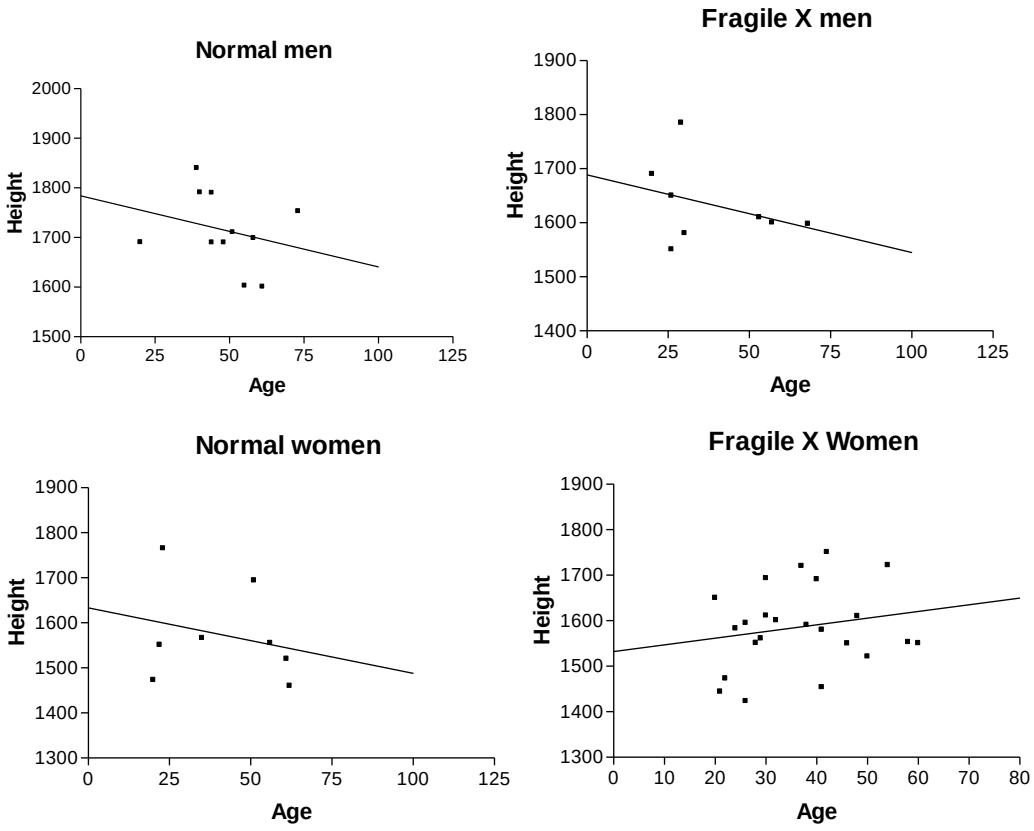

Figure 3. Scatter plots of height (mm) against age in men and women.

structures of the pedigrees according to Huggins and Loesch (1995). The first uses the models of Lange, (1978) and Hopper and Mathew (1982) which consider an additive genetic variance, a noon additive genetic or dominance variance, and the environmental variance. The second model considers phenotypic correlations between parent and offspring, between siblings, and between other relatives.

The basic model for the covariance matrix in the traits was $\Omega = 2\sigma^2_a\Phi + \sigma^2_d\Delta + \sigma^2_{ei}I$, where genetic variance included additive component, σ^2_a modelled using the kinship matrix denoted by $\Phi = (\phi_{i\ j})$ and dominance component, σ^2_d modelled using Jacquard's condensed coefficient of identity matrix, $\Delta = (\Delta i\ j)$. The environmental component in the covariance formula given above, σ^2_{ei}, represents individual environment. In order to take into account the common environment effects of siblings, which may be confounded with dominance variation, a dominance/common environment variance component σ^2_{dc} was considered rather than defining dominance as above, which replaced $\sigma^2_d\Delta_{i\ j}$ for siblings I and j.

A model for the covariance based on family relationships was also considered in order to examine possible deviations of this data from an additive model. In this model σ^2 denote the total variance, ρ_p denote the correlation between parent and offspring, ρ_s the correlation between siblings and ρ_o the correlation between other relatives. In order to take the extended family structure into account, ρ_o is taken to be the correlation between second degree relatives and the correlation between more distant relatives is taken to be $8 \times \rho_o \times \phi_{i\ j}$. The factor 8 was chosen as $\phi_{i\ j} = 1/8$ for second degree relatives such as grandparent and grandchild is ρ_o whilst that between third degree relatives such as cousins is $\rho_o/2$.

In this model, a difference between ρ_p and ρ_s suggest dominance deviation whilst a difference between ρ_p and $2 \times \rho_o$ suggest a correlation that is due to common family environment. Note that there could be many causes of observed difference between ρ_p and ρ_s , including non-genetic effects such as common sibling environment or a cohort effect. In order to establish if fragile X affects the values of correlations between relatives, the model was further extended by separating the correlations between normal pairs of relatives from pairs in which at least one individual is affected by fragile X.

The current data was analysed according to the application of these models and the resultant outcome is reported.

RESULTS

Ridge breadth

Based on the best fitting model, the robust estimates of parameters for the effect of fragile X and sex on the mean of ridge breadth are presented in Table 3. Tests involving intercepts and means are one sided whereas those concerning the slopes are two sided. It could be observed from the result in Table 3 that fragile X women have higher ridge breadth than normal and this similar trend exists for men although the difference is not statistically significant. Fragile X girls have higher intercepts than normal and fragile X boys show a contrast, there is no significant difference between fragile

Table 3. Robust estimate of the effect of age, sex and fragile X status on mean ridge breadth in adults and on the regression of mean ridge breadth on palm width (mm) on age in boys and girls.

Categories according to age, sex and fragile X status	Intercept (SE) $\alpha_{children}$	Regression (SE) $B_{children}$	Mean (SE) μ_{adults}
Normal men			586.2 (17.9)
Fragile X men			584.6 (31.4)
Normal boys	315.1 (184.1)	27.8 (27.6)	
Fragile X boys	262.4 (116.2)	33.9 (15.2)	
Normal women			512.5 (10.0)
Fragile X women			536.7 (13.3)
Normal girls	187.5 (176.1)	57.9 (26.5)	
Fragile X girls	445.3 (143.6)	23.0 (22.9)	

Table 4. Estimated variance component (a) and estimated total variance and correlations of ridge breadth between relatives with (bii) and without decomposition by fragile X status†.

a) Variance components		σ^2_e	σ^2_a	σ^2_{dc}
		3572.0 (59.8)	2767.0 (52.6)	3744 (61.2)
b) Pairs of relatives	Total variance σ^2	Parent-offspring ρ_p	Sibling-sibling ρ_s	Other ρ_o
bi) All	4309.0 (65.6)	0.32* (0.10)	0.004 (0.00)	0.35 (0.12)
bii) Normal-normal	4221.8 (65.0)	0.44 (0.19)	0.15 (0.02)	0.77**(0.59)
other	4541.0 (67.4)	0.27 (0.07)	0.17 (0.03)	0.24 (0.06)

† includes normal – normal, normal – fragile X and fragile X - fragile X siblings as other. *, ** P – values of comparisons are * < 0.01, ** <0.001

X and normal slopes for either sex.

The result of the covariance structure analysis showed that the genetic additive is significant (Table 4). This significance is explained by applying the simple variance component model to the pedigrees under study as shown in Table 4 by correlations between relatives. Equally significant correlations are observed in the parent-sibling pair and this is consistent with the model for additive inheritance (Table 4). In order to determine major fragile X gene influence, correlations were considered separately for normal-normal and for other pairs. Table 4 showed that, parent-offspring correlation is significantly greater than the value of sib – sib correlations and this is consistent with the additive inheritance model. The presence or absence of the fragile X cases in the pairings has minimal influence on parent-offspring and sib-sib correlations but a significant effect in other pairs of relatives in Tables. The value of normal other correlation is high in Table 4, indicating a significant contribution of the dominance component of covariance structure to the inheritance of ridge breadth in the pedigrees.

Height

The robust estimates of parameters for means of body height in fragile X individuals and their normal relatives are presented in Table 5. Fragile X men were shown to be significantly shorter than normal men. For women the reverse is the case, whereby fragile X women were taller than normal women, although the difference is not significant. The parameters of body height as a function of age showed that there is a statistically significant difference in the regression slopes between normal and fragile X boys although the cut-off age is clearly elevated in fragile X boys than in normal boys, growth in normal boys terminates about 4.2 years earlier than fragile X boys.

The results of fitting the covariance structure in Table 6 showed that genetic additive and environmental components of covariance are significant. The explanation for the presence of dominance in the covariance model for body height is sought by computing the correlations between relatives. As observed in the ridge breadth data, parent-offspring and sib-sib correlations are consistent with the additive model of inheritance, for all and normal pairs respectively. Therefore, it would appear from Table 6 that the additive effect of fragile X is the reduction of correlations observable when the pairings involve fragile X.

Testicular volume

The robust estimates of parameters for testicular volume in fragile X males and their normal male relatives presented in Table 7 show that testicular volume mean is

Table 5. Robust estimate of the effect of age, sex and fragile X status on mean height (in mm) in adults and on the regression of height (in mm) on age in boys and girls.

Categories according to age, sex and fragile X status	Regression (SE) $B_{children}$	Cut-off (SE) $\theta_{children}$	Adult mean (SE) $\mu_{children}$
Normal men			1714* (22.6)
Fragile X men			1633* (26.4)
Normal boys	54.5 (25.0)	14.6 (0.72)	
Fragile X boys	48.2* (19.2)	18.8 (0.44)	
Normal women			1573 (37.3)
Fragile X women			1581 (18.7)
Normal girls	35.6 (15.6)	18.0 (0.63)	
Fragile X girls	47.7** (9.98)	17.2 (0.37)	

*P < 0.05 for the comparison of the means and regression slopes. **P = 0.005.

Table 6. Estimated variance component (a) and Estimated Total Variance and Correlations of Height between Relatives With (bii) and Without Decomposition by Fragile X Status†.

a) Variance components		σ^2_e 16 642.9 (129.0)	σ^2_a 15682.8 (125.2)	σ^2_{dc} 14501.7 (120.4)
b) Pairs of relatives	Total variance σ^2	Parent-offspring ρ_p	Sibling-sibling ρ_s	Other ρ_o
bi) All	16029.6 (126.6)	0.40** (0.16)	0.59***(0.35)	0.18 (0.04)
bii) Normal-normal	25448.7 (159.5)	0.79***(0.62)	0.68** (0.46)	0.14 (0.02)
other	10265.5 (101.3)	0.36 (0.13)	0.40 (0.16)	0.14 (0.02)

† includes normal – normal, normal – fragile X and fragile X - fragile X siblings as other.*, ** P – values of comparisons are * < .01, ** <.001, *** < 0.0001

significantly greater in fragile X men than normal men. The parameters of testicular volume as a function of age showed that fragile X boys had higher intercepts than normal boys and this could be indicative of the differential observed in adults. This result is consistent with the clinical observation that orchidism is a frequent presentation in fragile X cases.

The results of fitting the covariance structure for the data presented in Table 8 showed contrast to the pattern observed in the ridge breadth and height data. In explaining the presence of significant dominance in the preferred model correlation computations among pairs of relatives reveal that parent-offspring correlations are significantly less than sib-sib correlations except in the normal pairings, thus producing deviation from a genetic additive model of inheritance. In order to examine if these observed effects are due to normal genes (or common sibling environment) or major fragile X gene, normal x normal and other pairs are considered separately. From the data in Table 7, it appears that for the normal pairs, parent offspring and sib-sib pairings are consistent with the additive model of inheritance, whereas fragile X causes the reduction of parent-offspring correlations.

DISCUSSION

The effect of fragile X on the mean values of one dermatoglyphic (ridge breadth), and two anthropometric (body height and testicular volume in males) measurements was demonstrated, where this effect is estimated against the background of the normal hereditary variations of these quantitative traits. The effectiveness of applying robustified likelihood function which simplifies the handling of outlying observations to the analysis of pedigrees was tested; particularly in this situation of small kindred, where sample size is not high.

The results of ridge breadth means and regressions confirmed the earlier findings of Huggins and Loesch (1995), based on simple comparisons between fragile X data and that of normal control samples which showed that fragile X individuals, especially female carriers have wider ridge breadth than the normal subjects (Loesch, 1986). The result of this analysis, which controlled for family factors and palm width, shows that fragile X has the effect of increasing ridge breadth. The effect of the expression of fragile X predominantly in females is at variance with the predicted model for the X-linked inheritance. It is possible that this observed increase in ridge breadth in females is due to the dosage effect of sex chromosomes on the value of this trait established in earlier studies (Penrose and Loesch, 1967), especially as the fragile X condition involves fluctuations in the magnitude of CGG repeats. On the other hand, the possibility of interplay of sex and genetic heterogeneity of the fragile X mutation cannot be exempted (Huggins and

Table 7. Robust estimate of the effect of age and fragile X status on mean testicular volume (in ml) in adults and on the regression of testicular volume (in ml) on age in boys.

Categories according to age, sex and fragile X status	Regression (SE) $B_{children}$	Cut-off (SE) $\theta_{children}$	Adult mean (SE) $\mu_{children}$
Normal men			24.0* (1.11)
Fragile X men			28.8* (1.60)
Normal boys	0.54 (0.30)	12.7 (0.88)	
Fragile X boys	0.47 (0.65)	23.7 (1.28)	

*P = 0.02.

Table 8. Estimated variance component (a) and estimated total variance and correlations of testicular volume between male relatives with (bii) and without decomposition by fragile X status†.

a) Variance components		σ^2_e	σ^2_a	σ^2_{dc}
		30.3 (5.50)	48.6 (7.00)	19.0 (4.36)
b) Pairs of relatives	Total variance σ^2	Parent-offspring ρ_p	Sibling-sibling ρ_s	Other ρ_o
bi) All	25.9 (5.09)	0.30 (0.09)	0.55* (0.30)	0.26 (0.07)
bii) Normal-normal	26.6 (5.16)	0.76**(0.58)	0.94**(0.89)	-0.74 (0.55)
other	11.7 (3.42	0.02 (0.00)	0.80* (0.63)	0.14 (0.02)

† Includes normal – normal, normal – fragile X and fragile X - fragile X siblings as other. *, ** P – values of comparisons are * < .01, ** <.001.

Loesch, 1995). In this case the mechanism of how the fragile X mutation leads to the specific characteristic of increase in dermal ridge breadth need to be fully understood if an acceptable explanation to be tenable. It is however inappropriate to draw any parallel between these two mechanisms from the existing data. In the height data, fragile X seem to have the effect of lowering body height in males. Similar trend observed in girls' height data is consistent with earlier studies. The reverse trend observed in adult females is not expected and may be attributable to cohort effect rather than a major indication. This is predicated on the observation of difference observed in the age cut-offs of girls, therefore implying that fragile X girls stop growing earlier than normal. It would appear from this data that boys grow at a lower, and the girls at a higher rate than their normal relatives and this is consistent with the earlier findings of Butler et al. (1992) and Huggins and Loesch (1995). The observation that growth in normal boys terminates about 4.2 years earlier than fragile X boys may not directly explain the observed differences in the means of adult mean. It could be concluded from this data that normal boys have a higher growth rate and therefore reach their peak body height earlier than fragile X boys. It was noted that even with 4.2 years extra growth the differential in mean height among adults giving an average increase of 4.2 × 54.7 = 228.9 mm is small compared to the adult mean differential of 81 mm. The observed significant difference in body height in adults may therefore be more related to growth rate rather than actual period of growth termination. Significant differences were observed in the slopes and cut-offs between normal and fragile X girls, which might be accountable for the differences observed in the adults.

However, to give more specific interpretation to these findings, the height as well bone age, need to be monitored longitudinally. And this would yield more accurate information on the growth pattern in relation to the onset, the rate, and the termination of skeletal maturity. An interesting aspect of the analysis applied in this study is that it allows for the estimation of the fragile X mutation on covariance between relatives as well as on the mean of the traits. Of interest is the observation that the fragile X alleles seem to lessen the contribution of the additive variance component in ridge breath, height and testicular volume, thus causing a deviation from the additive genetic model in contrast to the height and testicular volume data which tends toward an additive genetic model (Tables 6 and 8). Consequently the (narrow) heritability of height representing additive genetic effect based on the estimates of variance components is 0.50, which is appreciably lower than the values varying from 0.75 to 0.85 in other studies based on normal families (Tambs et al., 1992) and even lower than the narrow heritability of 0.58, deducible from the data of Huggins and Loesch (1995). Heritability for ridge breadth and testicular volumes are 0.55 and 0.43, 0.50 and 0.66 respectively. The author is not aware of any previous report on the heritability of testicular volume in fragile X pedigrees for comparison. Furthermore, by

separation of normal from other pairs of relatives, it was confirmed that the observed relative decline in the parent –offspring correlations may be largely attributed to a major fragile X gene in the three traits. It is probable that the effect of fragile X chromosome is caused by specific features of the abnormal gene containing the excessive number of the CGG triplet nucleotide repeats, which is further amplified in the offspring if transmitted trough the female (Glover-Lopez, 2006; Chiurazzi et al., 2003). This is what causes the anticipation phenomenon mentioned earlier whereby the severity of the fragile X increases in subsequent generations. Although the parent – offspring cohort effect may sufficiently explain the observed deviation from the perfectly additive model, it does not contradict the presence of male genetic dominance in body height postulated on the basis of the analysis of a large number of twins and their relatives (Tambs et al., 1992). However, using a relatively small samples as in the present study, and applying simple genetic models permitted the identification of large and obvious effects of such as those caused by abnormal genes. The results of this study emphasise the importance of identification of various types of effects in a family before drawing conclusions about the presence of genetic dominance in polygenic quantitative traits.

ACKNOWLEDGEMENTS

The author sincere thanks go to Dr. Hastings Ozwara of the Kenya National Museum for his contributions and support during the development of this manuscript. Same go to Tijmen Hilan for his accommodation and computer time at the initial part of data collation and analysis. Thanks to Edward, of Science journal (formally of the Biomedical primate research centre, Rijswijk, Netherlands, for the provision of graph pad prism software for scientific analysis.

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