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*Short Note*

## Estimates of Genetic Variance for Anterior Fontanelle Development in the NCPP Twin Population

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There are several dynamic influences on anterior fontanelle development in infants; among them, brain growth, dural attachments, suture development, and osteogenesis. It thus seems reasonable to hypothesize that variation in anterior fontanelle development between infants, related and unrelated, might have a significant genetic component. Anterior fontanelle size was quantitated by the method of Popich and Smith for 94 monozygotic (MZ) and 187 dizygotic (DZ) four-month-old twin pairs. The general model for estimating genetic variance from quantitative twin data was applied to MZ and DZ twins and then separately by chorion type. Since there were significant mean differences between blacks and whites, races were analyzed separately. The within-pair mean square estimates of genetic variance ( $\hat{G}_{WT}$ ) were highly significant for both blacks ( $P < 0.02$ ) and whites ( $P < 0.002$ ). Comparisons of means, total variances, and among-pair mean squares within races revealed no heterogeneity. There were also no significant chorion effects. Since the anterior fontanelle closes at around 1–1½ years of age, it was evaluated at age one in 95 MZ and 194 DZ twin pairs as a qualitative trait – ie, open vs closed, concordance vs discordance. There were no significant differences in proband concordance rates between MZ and DZ twin pairs for either blacks ( $P > 0.5$ ) or whites ( $P > 0.10$ ). Again, there were no significant chorion effects. These data suggest that anterior fontanelle developmental variation has a significant genetic variance component at four months of age but not at one year. This finding may be related to the rapid brain growth witnessed between birth and eight to nine months of age.

**Key words:** Anterior fontanelle, Genetic variance, Twins, Chorion effects

### INTRODUCTION

At birth the bones of the cranial vault are separated by dense connective tissue membranes termed sutures. Larger unossified membranous intervals, termed fontanelles, are found at the angles of the parietal bones. There are six fontanelles, one anterior midline, one posterior midline, and two, anterolateral and posterolateral, on either side of the midline. The anterior fontanelle (fonticulus anterior) is the largest. This lozenge- or diamond-shaped area is located at the junction of the sagittal, coronal, and metopic sutures. The anterior fontanelle is obliterated by ossification sometime during the first half of the second year of life.

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The flexible sutures and larger fontanelles allow for overriding of the bones to occur at birth, a normal process, and for rapid unrestricted brain growth during infancy and childhood. There are a number of dynamic influences on anterior fontanelle development in infants: brain growth, dural attachments, suture development, and osteogenesis. Bone growth is primarily passive in response to brain growth, and in this sense the brain acts as a functional matrix in determining the ultimate neurocranial growth [1]. Given this complex and dynamic developmental process, it seems reasonable to predict that variation in anterior fontanelle development between infants, related or unrelated, might have a significant genetic component.

Using a sample of monozygotic (MZ) and dizygotic (DZ) twins who did not have a major congenital malformation or more than one minor malformation as previously defined [5], we sought in this study to obtain an estimate of the genetic variance from quantitative anterior fontanelle data collected during the first year of life. In addition, the study was designed to determine the effects, if any, of chorion type on the variation in anterior fontanelle development of MZ twins.

## MATERIALS AND METHODS

This investigation is part of a larger ongoing study of children who were born to mothers registered in the NINCDS Collaborative Perinatal Project (NCP) [7]. The epidemiologic characteristics of twins born in the NCP have been previously described [5]. To summarize, 615 pairs of twins were born among 56,249 pregnancies with known outcome. The zygosity of 497 pairs was established by comparison of sex, nine polymorphic blood group systems (ABO, MNS, Rh, P, Kell, Lewis, Lutheran, Duffy, and Kidd), and gross and microscopic examination of the placenta. There were 188 MZ and 309 DZ twin pairs. Among the 188 MZ pairs, 117 were monozygotic (MC) and 56 dichorionic (DC). Chorion type in the remaining 15 pairs was uncertain.

At four months of age, and again at one year, the anterior fontanelle was determined to be open or closed by finger palpation. If open, the greatest anterior-posterior and lateral dimensions were measured and recorded to the nearest millimeter. These two measurements were added and divided by two, giving a single quantity, as suggested by Popich and Smith [8]. There were 94 MZ twin pairs and 187 DZ twin pairs who had (1) no major or more than one minor congenital malformation, (2) a known chorion type, and (3) anterior fontanelle measurements at four months of age. Measurements were made at one year for 95 MZ twin pairs and 194 DZ twin pairs who met the first two criteria. Of the 94 MZ twin pairs in the four-month sample, 58 were MC and 36 DC. Of the 95 MZ twin pairs in the one-year sample, 60 were MC and 35 were DC.

The general model for estimating genetic variance from quantitative twin data, as previously described by Christian et al [2], was applied to four-month-old MZ and DZ twins and then separately to MC and DC MZ twins and DZ twins. Using the among- and within-twin-pair mean squares, two independent estimates of genetic variance are obtained:  $\hat{G}_{WT}$  = within-DZ mean square - within-MZ mean square and  $\hat{G}_{AT}$  = among-MZ mean square - among-DZ mean square. For most cases,  $\hat{G}_{WT}$  is shown to be an adequate measure of genetic variance; however, if the total mean squares differ more than could be expected by chance, then the arithmetic mean of  $\hat{G}_{WT}$  and  $\hat{G}_{AT}$  must be used as an unbiased estimate of twin genetic variance [2]. Two-tailed F-tests were used to test for heterogeneity of the among-pair and within-pair mean squares of MC-MZ and DC-MZ anterior fontanelle size. Since the mean four-month anterior fontanelle size was significantly greater ( $P < 0.0001$ ) in blacks ( $2.79 \pm 1.33$  cm) than in whites ( $2.26 \pm 0.99$  cm), all analyses were performed by race. Male and female means were not significantly different ( $P > 0.70$ ), and thus the sexes were combined for analysis.

Since the anterior fontanelle closes between 1 and 1½ years of age, the trait at this age effectively becomes a discontinuous one, ie, open or closed. If both twins of a pair had either open or closed anterior fontanelles, that pair was recorded as concordant. If one twin of a pair was open and the other closed, that pair was recorded as discordant. Since all twins in the NCP population were ascertained independently, the proband concordance rates were calculated assuming complete ascertainment [4].

## RESULTS

The mean four-month anterior fontanelle size for each of the six race-twin type classes (Table 1) demonstrates that within race there was little difference between the various twin types with regard to average anterior fontanelle size.

Estimates of genetic variance from four-month-old white and black twins are presented in Tables 2 and 3. Using the total white MZ twin sample (Table 2), we found no evidence for heterogeneity for the total variances of MZ and DZ twins ( $P > 0.60$ ). In addition, the within-pair estimate ( $\hat{G}_{WT}$ ) of genetic variance was significantly different from zero ( $P < 0.002$ ). Comparing the MC-MZ and DC-MZ twin pairs separately with the DZ pairs resulted in genetic variance estimates only slightly different from the estimate obtained with the total MZ sample. Furthermore, two-tailed F-tests for homogeneity of variance revealed no significant differences between the MC-MZ and DC-MZ within-pair ( $F_{27,10} = 1.15$ ,  $P > 0.50$ ) and among-pair ( $F_{26,9} = 2.78$ ,  $P > 0.05$ ) mean squares.

Using the total black MZ twin sample (Table 3), we again found no evidence for total variance heterogeneity between MZ and DZ twins ( $P > 0.50$ ). The within-pair estimate ( $\hat{G}_{WT}$ ) of genetic variance was also significantly different from zero ( $P < 0.02$ ). As with whites, comparing the MC-MZ and DC-MZ twin pairs separately with the DZ pairs did not change the genetic variance estimates by an appreciable amount from the estimate obtained with the total MZ sample. Two-tailed F-tests for variance homogeneity revealed no significant differences between the MC-MZ and DC-MZ within-pair ( $F_{31,26} = 1.25$ ,  $P > 0.50$ ) and among-pair ( $F_{25,30} = 1.12$ ,  $P > 0.50$ ) mean squares.

Table 4 presents the analysis of proband concordance rates for white and black MZ and DZ twin pair anterior fontanelle status at one year of age. The proband concordance rates between MZ and DZ twin pairs were not significantly different for either white or black twins. Analyzing the rates separately for MC and DC-MZ twins did not reveal any significant chorion effects in either racial group.

TABLE 1. Mean Four-Month Anterior Fontanelle Size for Each Race-Twin Type Class

Whites				
	MC-MZ pairs	DC-MZ pairs	DZ pairs	
Number	27	10.0	88	
Mean (cm)	2.12	1.93	2.33	
SD	$\pm 1.03$	$\pm 0.67$	$\pm 1.01$	
$t'$		0.75	-2.02	
P		0.460	0.064	
Blacks				
	MC-MZ pairs	DC-MZ pairs	DZ pairs	
Number	31	26	99	
Mean (cm)	3.40	2.94	2.55	
SD	$\pm 1.30$	$\pm 1.35$	$\pm 1.27$	
$t'$		1.36	1.40	
P		0.179	0.171	

Note: Differences between the means were determined using the  $t'$ -test in the manner suggested by Christian and Norton [3].

TABLE 2. Estimate of Genetic Variance From White MZ and DZ Twin Pairs

	MZ	DF	DZ	DF
Number of pairs	37	—	88	—
Among mean squares	1.53	36	1.33	87
Within mean squares	0.29	37	0.70	88
Test of twin model:				
Sum of mean squares	1.82	49.28	2.03	158.95
			F' = 1.11	
			P = 0.671	
Estimate of genetic variance		Estimate	F	P
$\hat{G}_{WT} = WMS_{DZ} - WMS_{MZ}$		0.41	2.40	0.0019

TABLE 3. Estimate of Genetic Variance From Black MZ and DZ Twin Pairs

	MZ	DF	DZ	DF
Number of pairs	57	—	99	—
Among mean squares	3.25	56	2.61	98
Within mean squares	0.36	57	0.60	99
Test of twin model:				
Sum of mean squares	3.61	68.24	3.21	141.10
			F' = 1.12	
			P = 0.555	
Estimate of genetic variance		Estimate	F	P
$\hat{G}_{WT} = WMS_{DZ} - WMS_{MZ}$		0.24	1.68	0.017

TABLE 4. Proband Concordance Rates for Anterior Fontanelle Development at Age 1 Year

	White pairs		Black pairs	
	MZ	DZ	MZ	DZ
No. concordant	29	60	45	82
No. discordant	7	27	14	25
% concordant	89	82	87	87
$\chi^2$	1.41		0.02	
P	>0.10		>0.50	

## DISCUSSION

From this investigation of anterior fontanelle development during the first year of life, the following conclusions may be drawn:

1. There are significant mean differences in anterior fontanelle size between blacks and whites at four months of age.

2. At four months of age in both races, anterior fontanelle developmental variation has a significant genetic variance component. That is, the proportion of the total anterior fontanelle developmental variation in this population that can be attributed to this population's genetic variation is considerable.
3. Since the proband concordance rates for one-year-old MZ and DZ twin pairs of both races were not significantly different, this suggests that variation in closure at one year of age is associated primarily with environmental variation.
4. There was no evidence of significant chorion effects either at four months or at one year of age for either racial group.

The changing magnitude of the genetic and environmental components of the total variation from four months to one year of age is interesting but enigmatic. This apparent difference may be due to lack of sensitivity of the concordant measure to detect true differences, and a prospective study of closure using shorter time intervals might well be more informative. Alternatively, perhaps this phenomenon is related to the dynamics of brain growth. The cessation of cell proliferation in whole brains occurs six to eight months postnatally [6]. Since the brain, in effect, acts as a functional matrix in determining neurocranial development [1], the effects of variation in brain growth velocity would be much more apparent at four months than at one year. If one is allowed to speculate that variation in brain growth velocity between individuals in a population has a significant genetic variance component, then the results of this study are potentially explainable. By one year of age variation in brain growth would be dramatically reduced, and thus neurocranial development would be more a result of environmental factors than the genetic program of neural cytological, histological, and morphological differentiation.

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