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Familial Studies of Monozygotic Twinning

Wendy Olson Segreti, BA, MA, Phyllis M Winter, BS, and Walter E Nance, MD, PhD

Genetic studies on monozygotic (MZ) twins have generally shown no increase in the repeat frequency of twinning and no racial differences in the incidence of MZ twins [Bulmer, 1970]. Nevertheless, families continue to be reported in which there have been multiple cases of MZ twins or the coincidence of MZ and dizygotic (DZ) twinning [Harvey, Huntley, and Smith, 1977; Shapiro, Zemek, and Shulman, 1978]. To explore the possibility that genetic factors might play a role in the etiology of a particular subset of MZ twins, we have investigated the occurrence of twins in the first-, second-, and third-degree relatives of 343 sets of MZ twins in relation to racial background, placental type, and age of mother.

Family histories were available on 307 MZ nonblack and 36 MZ black twin pairs that had been collected by one of us at Indiana University and the Medical College of Virginia. The sample included 148 male pairs ranging in age from newborn to 82 years and 195 female pairs ranging from newborn to 69 years. Zygosity was determined in all probands by analysis of eight different blood groups.

The results of a systematic inspection and histologic examination of the placenta were available on a subset of 80 pairs and some information about placentation was known on an additional 81 pairs. The classification of the twins by placental type is shown in Table I. The mean maternal age did not vary with placental type.

The number of twin pairs in the families of MZ twins classified by placental type is shown in Table II. Overall, there were 156 sets of twins in 106 (or 31%) of the families. The average number of additional twins in the family was remarkably similar in twins with different placental types and there was a uniform excess of twins in the mother's side of the family. To what extent the latter

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TABLE I. Distribution of Placental Type and Mean Maternal Age

Placental type	Nonblack twins		Black twins	
	No. of pairs	Mean maternal age ± SE	No. of pairs	Mean maternal age ± SE
MCMA	3	27.3 ± 3.5	3	22.3 ± 1.7
MCDA	27	25.4 ± 0.9	15	25.6 ± 1.6
MC?A	1	18	2	21.5 ± 4.5
DCDA	12	26.8 ± 1.8	8	23.3 ± 2.3
Unknown	7	29.3 ± 2.4	2	18.5 ± 1.5
Total	50	25.4 ± 1.9	30	22.2 ± 1.2

TABLE II. Number of Twin Pairs in the Families of MZ Twins

Placental type	No. of index pairs	No. of twin pairs among			Twin pairs per kindred
		Maternal relatives	Paternal relatives	Other[a] relatives	
MCMA	16	4	2	1	0.44
MCDA	52	17	12	1	0.58
MC?A	45	11	8	–	0.42
DCDA	48	14	8	2	0.50
Unknown	182	32	27	17	0.42

[a]Includes sibs, children, nephews, and nieces of probands.

finding reflects ascertainment bias is not known with certainty. However, to investigate ascertainment bias, we compared newborn twins who represented consecutive births with all other twins many of whom were self-selected volunteers. The two groups did not differ in placental type or maternal age. The newborn twins had just as high a twinning rate as the other twins, who might have volunteered on the basis of an excess of twins in their family.

The overall mean age of the mothers at the time of the birth of the probands was 24 years. The distribution of familial twins and probands according to the age of the mother is shown in Table III. In our sample 168 sets of twins had mothers over age 24, 128 sets had mothers less than or equal to 24, and 47 maternal ages were unknown. No conspicuous differences were noted in the distribution of placental types in the two maternal age groups.

Table IV presents the racial distribution of familial twins. Although not statistically significant, an excess of twins in the maternal relatives was observed in both racial groups, and the overall frequency of twins in the family was significantly greater in blacks than in nonblacks, $p > 0.01$. The zygosity of the other

TABLE III. Distribution of Familial Twins and Probands According to the Age of the Mother

Maternal age at probands' birth	No. of probands	Maternal twins	Paternal twins	Other twins[a]	Total	Twin pairs per kindred
> 24	168	29	28	11	68	0.40
≤ 24	128	47	29	5	81	0.63
Unknown	47	2	–	5	7	0.15
	343	78	57	21	156	0.45

[a]Includes sibs, children, nephews, and nieces of probands

TABLE IV. Racial Distribution of Familial Twins

Race	No. of probands	Maternal twins	Paternal twins	Other twins[a]	Total	Twin pairs per kindred
Nonblack	307	60	48	19	127	0.41
Black	36	18	9	2	29	0.81
Total	343	78	57	21	156	0.45

[a]Includes sibs, children, nephews, and nieces of probands.

twins in the probands' families also differed in the two racial groups. As shown in Table V, among pairs in which the zygosity was known many more of the twins were dizygotic in the families of black probands, $p > 0.01$.

The data in Table VI shows the type of twinning in 106 families in which additional twins occurred. It is interesting to note that six families already contained both MZ and DZ twins within three degrees of kinship. Overall, 17% of the families had other MZ twins and 44% had other DZ twins. A total of 34 other sets of twins were found among the first-degree relatives (parents, sibs, and children of probands), 59 among second-degree relatives (grandparents, uncles and aunts, nieces and nephews of probands), and 63 among third-degree relatives (first cousins of the probands).

The rate of twinning per thousand births was calculated for the 343 MZ twin pairs and comparisons were based on the general frequency of MZ and DZ twinning observed by Bulmer in 1970. Using these data, the expected number of twins in the family members of the black and nonblack index cases could be calculated. As shown in Table VII, the ratio of observed to expected was remarkably similar in the two groups. The twinning rates per thousand for this sample were 1.6 times greater than expected for both blacks ($p > 0.01$) and nonblacks ($p > 0.005$).

TABLE V. Distribution of Familial Twins by Zygosity and Race

Zygosity	Race		Total
	Black	Nonblack	
MZ	1	26	27
DZ	18	51	69
Unknown	10	50	60
Total	29	127	156

TABLE VI. Types of Twinning Found Among 106 Families With Positive Family Histories of Twinning

Twins among relatives	No. of families	%
MZ only	18	16.98
DZ only	47	44.34
MZ and DZ	6	5.66
Unknown	35	33.02
Total	106	100.00

TABLE VII. Frequency of Twinning With First Three Degrees of Kinship in 343 MZ Twin Pairs

	Black	Nonblack
No. of probands	36	307
No. of relatives	1,015	6,788
Expected twins/1,000 among relatives	19.5	11.5
Observed twins/1,000 among relatives	31.5	18.5
Observed/expected	1.6	1.6

Several kindreds were particularly informative. In six families one member of a female MZ pair gave birth to MZ twins. In a seventh, #1885 shown in Figure 1, a mother had identical twins by two different husbands. These findings suggest that the genotype of the mother may be of primary importance in familial MZ

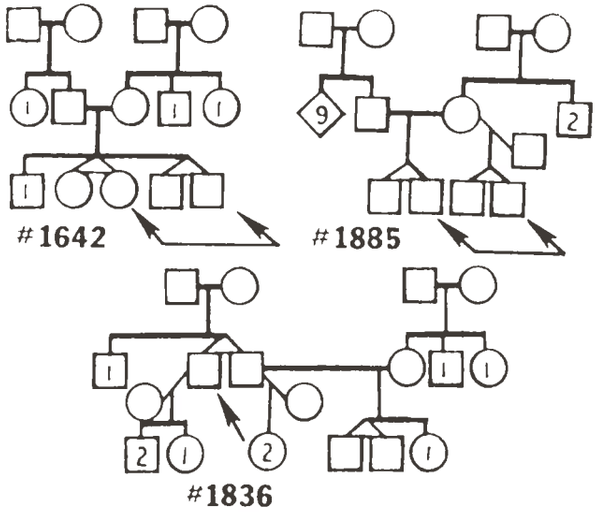

Fig 1. Three pedigrees illustrating variability in familial MZ twinning. Case #1642: two sets of MZ twins with different placental types within a sibship (females MC-DA, males MC-MA). Case #1885: two sets of MZ twins having the same mother and different fathers. Case #1836: male-to-male transmission of MZ twinning.

twinning. On the other hand, the observation of a single case in which an MZ father had MZ sons, #1836, clearly indicates that familial MZ twinning is not confined to matrilineal relatives. Finally, the third family, #1642, is of importance because placental examinations were available on both sets of MZ twins that were born to one mother. The older set was monochorionic-diamnionic while the younger was monochorionic-monoamnionic, and exhibited tangling of the cords at birth. This family demonstrates that even when MZ twinning recurs in a family, the stage at which twinning occurs may not be the same.

Our study supports the view that in some families genetic factors may contribute to the occurrence of MZ twins. The causes of MZ twinning in man remain somewhat obscure and it seems likely that most cases represent sporadic events. Harvey, Huntley, and Smith [1977] have suggested that familial MZ twinning may have a monogenic basis and can be transmitted by either sex. The same vertical mode of transmission of MZ twinning by either males or females is prevalent in our larger sample, thereby supporting the thesis of a single dominant low-penetrant gene effect. This gene is apparently not functioning to control the time of division of the zygote, since placental types can vary within a family.

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