A Statistical Study of Half-Sibships Born to Parents Affected with Huntington's Disease

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A comparative study of half-sibships liable to inherit a dominant autosomal disorder from a common affected parent is of interest when the effect of the genetic contribution of the healthy parents to its manifestation in heterozygotes is considered. The possibility that allelic genes are responsible for the major clinical forms of Huntington's disease, namely the juvenile, Westphal, and classical variants, has been raised following the demonstration by Penrose (1948) that the variable age at onset of muscular dystrophy could be accounted for in these terms. The plausibility of this hypothesis was reduced when Byers and Dodge (1967) reported the occurrence of two childhood cases of Huntington's disease in their family B; the propositi were offspring of a choreic man by different wives. As only 5–10% of all cases of the disorder begin before adulthood (Bruyn, 1968), the probability that each woman bore the modifying gene is low.

Half-sibship data are also relevant to other hypotheses, such as the influence of parental age on the mode of onset. For example, if advancing age of an affected parent at conception predisposes to manifestation of the juvenile form, a higher incidence of childhood cases would be expected among the progeny of second than first marriages.

While assembling published pedigrees of Huntington families for statistical analysis, a number of half-sibship pairs were encountered. It was thought that a study of these might provide further information on the possible roles of allelic genes and parental age. The results obtained form the basis of the present paper.

Subjects and Methods

From a survey of the accessible literature, over 1500 sibships containing at least one subject with Huntington's disease were collected. Of these, 35 pairs of half-sibships each having a common choreic parent were

assembled for analysis. Details of their composition are listed in Table I. Two sibship pairs (9 and 12) were unusual in that both parents of the affected parent were choreic.

Analysis of variance by the weighted method for $r \times 2$ tables with disproportionate subclass numbers (Steel and Torrie, 1960) was used to determine variations in age at onset of symptoms and at death within and between half-sibships. Intraclass correlation coefficients and their standard errors were calculated by the semi-weighted method of Smith (1957). Heterogeneity of frequencies and goodness-of-fit estimations were made using the G-test (Sokal and Rohlf, 1969). Yates' correction was applied to all 2×2 contingency tables.

Results

Ascertainment. An obvious source of ascertainment bias is the failure to record affected siblings of second marriages because of their younger age in contrast to their half-sibs born during first marriages. Some evidence that this is unlikely to be serious in the present material is afforded by a comparison of proportions of affected siblings. The ratios of the numbers of affected to total offspring, summed over all half-sibships, was 0.75 ± 0.27 for first marriages and 0.66 ± 0.29 for second marriages. This difference is not significant. Supporting evidence is provided by the fact that only two sibship-pairs (nos. 30 and 32) were not succeeded by another generation, 11 were succeeded by 1 generation, 14 by 2 generations, 3 by 3 generations, 3 by 4 generations, and 2 by 6 generations. The great majority of families were therefore reported after the time when symptoms might have been expected to appear.

Clinical Variants. Of the 127 persons with Huntington's disease, in only 22 cases were clinical details adequate to enable identification of the presenting form. These consisted of 7 juvenile, one Westphal, and 14 classical cases. In the last, choreiform movements and mental disturbances were coincident 7 times, chorea alone was present 3

TABLE I
DETAILS OF HALF-SIBSHIPS

Sib-pair No.	First Marriage			Common Affected Parent	Second Marriage			Reference
	Known Choreics		Total Sibs		Known Choreics		Total Sibs	
	Males	Females			Males	Females		
1	2	2	7	Father	1	2	3	Peretti (1885)
2	0	2	4	Father	1	0	5	Hoffmann (1888)
3	0	1	2	Mother	0	1	4	Menzies (1892)
4	0	1	1	Mother	1	0	1	
5	1	0	1	Father	0	1	2	Müller (1903)
6	1	0	1	Father	1	0	1	Hathie (1909)
7	0	1	6	Father	1	1	4	Muncey (1916)
8	1	0	1	Father	0	1	2	
9	1	0	1	Father	1	0	3	
10	1	1	2	Father	0	1	3	
11	1	1	2	Father	3	2	6	
12	0	1	1	Mother	0	1	2	
13	1	0	1	Mother	2	1	6	Riggenbach and Werthemann (1933)
14	1	0	1	Mother	0	1	1	Bell (1934)
15	1	0	2	Father	2	0	3	Frank (1937)
16	0	2	3	Father	1	0	5	Entres (1940)
17	1	1	2	Mother	1	1	5	
18	2	2	9	Father	1	2	4	Panse (1942)
19	1	1	4	Mother	2	2	7	
20	1	1	3	Father	0	2	3	Frets (1943)
21	0	2	3	Mother	5	3	10	Brothers (1949)
22	0	1	3	Mother	0	1	6	Ørbeck and Quelprud (1954)
23	1	0	2	Mother	3	0	4	
24	1	0	2	Mother	0	1	2	
25	0	1	1	Mother	1	0	1	Pearson and Petersen (1954)
26	1	0	2	Father	0	2	3	Pleydell (1954)
27	1	1	2	Father	1	3	4	Brothers and Meadows (1955)
28	0	1	1	Mother	1	1	2	
29	1	3	4	Mother	0	1	1	Chandler, Reed, and de Jong (1960)
30	1	0	2	Father	1	0	1	Byers and Dodge (1967)
31	0	1	2	Mother	1	1	3	Moody (1967)
32	1	1	2	Mother	1	0	1	Delmas-Marsalet <i>et al</i> (1968)
33	0	1	1	Mother	3	2	9	Fraser and Updike (1969)
34	1	1	6	Father	1	1	2	Petit (1969)
35	0	1	1	Mother	1	0	4	Reisman and Matheny (1969)
Totals	24	31	88		37	35	123	

times, movements preceded mental signs twice, and followed them twice. In addition to the family data of Byers and Dodge (1967) already noted, two half-brothers with ages at onset of 5 and 20 years were reported by Delmas-Marsalet *et al* (1968). However, the onset age of the elder boy is close to adulthood and his symptoms could be regarded as an early presentation of the classical picture. Three of the juvenile cases occurred in first marriages and 4 in second marriages. In half-sibships 1, 2, and 28, the classical type alone is found in each pair; however as about 80% of all cases present in this way, these findings are not unusual.

Differences in Mean Numbers of Offspring. From Table I 6 significant differences emerge. In first marriages, the mean number of affected sons of choreic fathers exceeds the mean number of affected sons of choreic mothers ($t=2.76$, $p<0.01$) and the mean number of all offspring of choreic

fathers exceeds the mean number of all offspring of choreic mothers ($t=2.08$, $p<0.05$). In first marriages of females, the mean number of affected daughters is higher than the mean number of affected sons ($t=2.39$, $p<0.05$). Concerning the progeny of second marriages of affected females, the mean numbers of choreic sons and total sibs exceed those of first marriages ($t=2.28$, $p<0.05$ and $t=2.74$, $p<0.01$, respectively). When offspring of both parents are pooled, the mean number of children resulting from second marriages exceeds that of children resulting from first marriages ($t=2.01$, $p<0.05$).

Frequency Differences among Offspring of each Marriage. Offspring distributions of choreic parents common to each marriage are given in Table II. The number of children of various classifications born to mothers in second marriages is never exceeded by those born to mothers in first

marriages. The result is that mothers have twice the number of offspring in second as in first marriages, whereas fathers have the same number in each marriage; this heterogeneity is significant. A feature of the frequencies of total offspring of first marriages is their deviation from the sex ratios of affected parents. No such bias occurs in the progeny of second marriages.

Frequency Differences among Sib-pairs of each Marriage. To test whether sex-limitation occurred to any extent within sibships, the number of affected sib-pairs was counted and grouped according to parentage and marriage as shown in Table III. Frequency tests revealed significant heterogeneity to exist between marriages when mothers were affected and when the data were considered as a whole. Goodness-of-fit tests demonstrated a significant deficiency of like-sexed pairs in first marriages and in second marriages of choreic mothers. When data for both marriages were combined, sib-pair distributions derived from affected fathers did not differ significantly from those of mothers. This also held true if data of half-sibship pairs were combined and related to parentage. Examination of sib-pairs made up from all children, regardless of health, disclosed no appreciable deviation from the expected proportions.

TABLE II
DISTRIBUTION OF OFFSPRING OF CHOREIC PARENTS IN FIRST AND SECOND MARRIAGES

Offspring	First Marriage		Second Marriage	
	Father	Mother	Father	Mother
Affected sons	16	8	15	22
Affected daughters	14	17	18	17
Affected offspring	30	25	33	39
Unaffected offspring	7	2	7	12
Offspring of unknown state	17	7	14	18
Total offspring*	54	34†	54	69

* Heterogeneity between parents and marriages: $G(1 \text{ df}) = 5.61$, $p < 0.02$.

† Proportion of offspring in first marriages differs significantly from the affected parent sex-ratio of 17:18, $G(1 \text{ df}) = 5.80$, $p < 0.02$.

Affected half-sibs paired between marriages failed to yield any significant differences when compared with respect to sex of parent and conformity to expected ratios.

Comparison of Ages at Onset and at Death.

By analysis of variance it was found that age at onset did not vary significantly between half-sibships or marriages. Age at death varied significantly ($F = 5.92$, 10 df, $p < 0.005$) between half-sibships adjusted for marriages but not between marriages adjusted for half-sibships. Interaction was not significant in either analysis. When half-sibships were pooled, mean ages at onset and at death of males and females, of subjects inheriting their disease from fathers and mothers, and of progeny of first and second marriages were not significantly different. Taking the material as a whole, the following means and standard deviations, in years, were obtained: age at onset of 52 sibs, 32.8 ± 13.3 ; age at onset of 8 parents, 36.5 ± 7.2 ; age at death of 53 sibs, 48.4 ± 14.9 ; age at death of 20 parents, 55.4 ± 14.3 ; duration of disease in 33 sibs, 14.8 ± 7.7 ; duration of disease in 8 parents, 14.9 ± 6.8 . None of the differences between generations was significant.

Correlation Coefficients. The following ratios were calculated for each half-sibship: $CM/(CM + CF)$, $CF/(CM + CF)$, CM/T , CF/T , and $(CM + CF)/T$, where CM denotes the number of choreic males, CF the number of choreic females, and T the total number of persons in a half-sibship. Product-moment correlation coefficients for each ratio were estimated between first and second marriages. No significant correlations were found when offspring born to affected parents of each sex were analysed separately or together. The highest coefficient obtained, 0.444 for $(CM + CF)/T$ in children of affected mothers, failed to reach the 5% level of probability. The coefficient for the same ratio in children of affected fathers was -0.082 , but the difference between the values was not significant.

TABLE III
DISTRIBUTION OF AFFECTED SIB-PAIRS IN FIRST AND SECOND MARRIAGES

Affected Parent	First Marriage			Second Marriage		
	Brother-Brother	Brother-Sister	Sister-Sister	Brother-Brother	Brother-Sister	Sister-Sister
Father	2	13	4	4	15	8
Mother†	0	6	4	18	30	5*
Total**	2	19	8†	22	45	13

Frequencies of sib-pairs within marriages and parents differ significantly from the expected 1:2:1 ratio: * $G(2df) = 8.73$, $p < 0.02$; † $G(2df) = 6.69$, $p < 0.05$.

Heterogeneity within parents between marriages: ‡ $G(2df) = 10.33$, $p < 0.01$; ** $G(2df) = 6.76$, $p < 0.05$.

TABLE IV
CORRELATION COEFFICIENTS BETWEEN AFFECTED
HALF-SIBS OF FIRST AND SECOND MARRIAGES

	Age at Onset	No.	Age at Death	No.
Males	0.402	3	0.806†	12
Females	0.162	9	0.709*	8
Half-sibs of opposite sex	0.541	12	0.180	14
Offspring of affected fathers	0.649*	11	0.269	18
Offspring of affected mothers	0.167	13	0.703†	16
All offspring (simple correlation)	0.508*	24	0.506†	34
All offspring (partial correlation)	0.659†	17	0.474†	33

* $p < 0.05$; † $p < 0.01$.

TABLE V
CORRELATION COEFFICIENTS BETWEEN AFFECTED
PARENTS AND AFFECTED OFFSPRING OF FIRST
AND SECOND MARRIAGES

Marriages	Age at Onset	No.	Age at Death	No.
First	0.678*	10	0.415	21
Second	0.613†	14	0.018	22
Both	0.631‡	24	0.167	43

* $p < 0.05$; † $p < 0.02$; ‡ $p < 0.001$.

Table IV summarizes the correlations between marriages of ages at onset and at death of various types of subjects. All coefficients were positive and 6 of the 12 were significantly different from zero. Age at death of half-sibs of the same sex is highly correlated; this is not so when the sexes are different. The correlation coefficient found between males is significantly higher than that found between males and females ($p < 0.04$). A noteworthy feature is the similarity in values found for ages at onset and death of all offspring. However as the affected parent contributes to these correlations, parent-offspring correlations were also calculated (Table V) and the partial correlation coefficients reported in Table IV allow for these.

Eight correlation coefficients in Table IV were of significant magnitude and none of these differed significantly from 0.5. In Table V, each coefficient relating to age at onset was significantly higher than zero. Age at death of parents and offspring of first marriages was not significantly associated and the correlation coefficient did not differ significantly from 0.5, but for parents and offspring of second and both marriages the coefficients differed significantly from 0.5 ($p < 0.02$) but not from zero.

Because the variances of ages at onset and death among half-sibships had been found to exceed the variances within half-sibships, some degree of intraclass correlation was implied in each case. When marriages were combined and each of the two half-sibships treated as single sibships, signi-

ficant intraclass correlation coefficients were calculated for age at onset (0.478 ± 0.173) and age at death (0.582 ± 0.144). Numbers were insufficient to carry out the estimation within marriages.

Discussion

If one half-sibship shows no appreciable difference in frequency of a given attribute from the other, allelic genes may exert an equal or no effect. If significant differences do occur, such genes in the unaffected parents could be diverse. These simple expectations will be disturbed by factors such as nonallelic modifiers and environmental effects. It follows that the occurrence in sibship-pair no. 30 and possibly no. 32 of the juvenile variant in half-sibs does not provide sufficient evidence to reject the hypothesis that the clinical form of Huntington's disease is determined by the presence of a particular allelic genotype.

Virtually all of the 6 anomalies in half-sibship composition derived from Table I can be attributed to the deficiency of affected sons born to females in first marriages. No explanation can be offered for this, except to note that it is consistent with the reported tendency of choreic parents to produce an excess of affected sibs of the same sex as themselves (Bell, 1934).

The other significant results can be conveniently grouped into those found within marriages and those found between marriages. In the former category, the fewer children born to affected mothers than to fathers in first marriages is interesting. This may be because the average duration of second marriages of choreic females exceeds that of their first marriages whereas marriages of choreic men were of comparable mean duration. If this is so, it is not clear whether or how it relates to the asymmetrical distributions of sib-pairs in Table III. One possibility is that these arise from sampling bias due to the fact that half-sibships are on the average smaller in size than sibships resulting from single marriages.

More directly relevant to the design of the investigation and to the possible role of parental age are the differences and correlations observed between marriages. The heterogeneous distributions of affected sib-pairs derived from mothers and both parents (Table III) are likely to be due to the excess of male sibs in second marriages compared with first marriages. The large number of half-sibships containing both sexes and the corresponding small number of single-sex half-sibships with more than one sibling confirm the implications of Table III that familial sex-limitation does not operate to an appreciable extent.

The higher correlations found in Table IV for age at death between half-sibs of the same sex than for those of different sex and the apparently diverse effects of choreic parents are noteworthy. It will be important to establish whether these apply to intra-class correlations in an adequate sample of sibships. Also of interest is the relative proximity to 0.5 of the coefficients for age at onset and age at death found between choreic offspring of each marriage by simple and partial correlation. Bell (1942) has reported a value of 0.465 based on 442 sib-pairs for age at onset and a value of 0.521 based on 278 pairs for age at death. Both are similar to the coefficients presented in Table IV. A coefficient close to 0.5 is to be expected for sib-sib correlations if Huntington's disease is attributable to one main gene with several modifiers (Haldane, 1941) or to a number of mimic genes, each having its own age at onset or age at death distribution (Harris and Smith, 1948). The theoretical analysis by Burch (1968) of age at onset distributions would appear to favour the latter conclusion.

The position is less clear with respect to parent-child correlations. In theory these provide a convenient means of testing for the presence of allelic modifying genes. A zero correlation would be expected if they exert an effect on age at onset or at death (Penrose, 1948), whereas a correlation of 0.5 would be expected from the action of a single gene in concert with a number of independent nonallelic modifiers (Haldane, 1941). A number of separate main genes, each producing a characteristic age distribution, would also give rise to a value near 0.5 (Harris and Smith, 1948). The results in Table V suggest that age at onset is not determined by allelic genes, but that they could account for the observed age at death correlations between parents and offspring. This is subject to an element of doubt because the coefficient calculated for first marriages (0.415) does not differ significantly from 0.5.

It is concluded from the present results that allelic genes play no great part in modifying the age at onset of symptoms but that they cannot be excluded from affecting age at death and the clinical form of the disorder. Differences between variables associated with first and second marriages appear to be explicable in terms of sampling bias or the possibility that first marriages of choreic women are of shorter duration. This leaves little room for other explanations such as the effects of parental age.

Summary

To examine the possible effects of allelic modifying genes and parental age, 35 pairs of half-sibships

derived from a common parent affected with Huntington's disease were compared. There was insufficient evidence to exclude the hypothesis that allelic genes determine the type of clinical symptoms. Distributions of affected offspring expressed as a function of sex of parent and marriage number yielded evidence of heterogeneity which was largely due to the disproportionate numbers of offspring born to choreic women in each marriage. From results of correlation analyses it is concluded that allelic genes play little part in determining age at onset but could affect age at death.

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