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Evidence of genetic heterogeneity in Huntington's chorea

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SUMMARY In an extensive study of Huntington's chorea in Queensland evidence was found to support an old observation that the magnitude of the variation in the symptom complex of the disease between different families is sufficient to suggest that there may be more than one form of Huntington's chorea allele present in the community. Analysis of data concerning age at onset indicates that at least two separate forms of the disorder may exist.

It is generally accepted that Huntington's chorea is a single entity (McKusick, 1971). Reed and Chandler (1958) considered that the evidence from the data obtained during their survey in Michigan favoured the hypothesis that a single mutant gene is responsible in all cases. Bruyn (1968) in his monumental review accepts that there are three forms of the disorder: the classical form, a juvenile form, and the form he describes as the Westphal variant. However, he describes these variants as occurring in sibships where other cases have shown the features of the more common classical form of the disease, thus indicating a single mutant gene with varying expression in different individuals. Myrianthopoulos (1966) accepts that Huntington's chorea of childhood is a separate entity, but notes that these clinically peculiar cases are children born to choreic parents in families with Huntington's chorea and hence by implication represent the varying expressivity of the mutant allele.

Yet astute observers long ago recognized that the disease tended to run a different course in different families. Davenport and Muncey (1916) coined the term 'biotype' to describe the various strains as they occur in separate families. The term was created on clinical impression alone, and later workers, notably Chandler, Reed, and De Jong (1960) failed to confirm this impression in their Michigan study. Yet the impression remains, particularly among clinical workers (Bittenbender and Quadfasel, 1962; Müller-Küppers and Stenzel, 1963) that familial variations in symptom complexes do occur and may have a basis in the genetic entity giving rise to this disease. It is the purpose of this communication to re-examine this problem in the light of data obtained during an extensive clinical and epidemiological survey of Huntington's chorea in Queensland.

METHOD OF STUDY

During the years 1969 and 1970 an attempt was made to locate and interview every case of Huntington's chorea in Queensland, Australia, to obtain details of their family trees and to classify all living members of the families at risk. Notifications of families were obtained from many sources, and multiple ascertainment of kindreds and even of patients was the rule, rather than the exception, as was intended and which suggests a very complete ascertainment of all families with the disorder. Dr. Neville Parker's (1958) detailed and extensive pedigrees were obtained, the members of these families were checked, and the pedigrees were brought up to date. A personal approach was made to every medical practitioner specializing in a field which it was judged might include some cases of Huntington's chorea. In this way every psychiatrist, neurologist, neurosurgeon, and geriatrician practising in Queensland was approached for information concerning cases suffering from the disease. An approach was made to all general practitioners via the Australian College of

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General Practitioners for information on families or cases of the disease, and a personal search of the wards of the state's psychiatric institutions and individual approaches to the medical and nursing staff of each hospital, nursing home, or organization concerned in any way with the care of patients in the State of Queensland were made to locate further cases.

Each of the patients located, and each of the family members resident in Queensland who could have been at risk of developing the disease was examined personally as far as this was possible, and, in addition, extensive interstate travel in New South Wales, Victoria, and the Australian Capital Territory was involved in the follow-up of family members. It was found unsatisfactory to rely on medical reports, nor was it possible to make use of other personnel, medically trained or otherwise, as in such circumstances gross misclassification was frequent and pedigree data were most inadequately recorded. The results are thus those of a personal series collected by one of us (D.C.W.). All but four of the Huntington's choreics listed as living at the commencement of the study have been seen by one of us and these four have been seen by associates working on this study, but have not been seen by us for various reasons, principally because of distance. In regard to the pedigree data, much of the material has, for lack of other means of checking, been obtained by word of mouth from surviving relatives, but in the cross-correlation of the details given by various family members an apparently reliable history generally appears. In most cases the histories are internally consistent, and only where this is so have the data been included for analysis in this report. A summary of the data is set out in the Appendix.

COMPOSITION OF SAMPLE

Forty-seven separate kindreds were ascertained that were not definitely linked to a common ancestor. Among these a total of 108 cases of Huntington's chorea living on 1 January 1969 were examined. The family origins could be traced back only a few generations with certainty in most cases, and some of the kindreds may therefore have represented branches of a single larger pedigree. Their origins as determined, are set out in Table 1 and represent a fair approximation to the known proportionate ancestry of the Queensland population. There was only one representative of the large family detailed by Brothers (1949). Altogether some details were obtained concerning a total of 287 cases of Huntington's chorea belonging to these families.

TABLE 1

ORIGINS OF EARLIEST KNOWN CARRIER IN FAMILIES STUDIED

Australia		*Overseas*	
Queensland	8	England	13
New South Wales	7	Scotland	6
Victoria	4	Ireland	5
		Sweden	1
		Germany	1
		Malta	1
		Russia	1

CLINICAL EVIDENCE OF VARIATION BETWEEN KINDREDS

Early in the investigation it became obvious that on clinical grounds it was easy to recognize that the disease ran a similar course in each family and that the symptom complex varied from one family to another. There were families in whom the disease was severe with gross chorea, families in whom the disease was no more than a presenile dementia, families in whom intellectual function was well preserved until old age, and so on. In other words, to a clinician it was obvious that at the clinical level the concept of a 'biotype' had justification. The major measurable quantities such as age at onset, age at death, and duration of symptoms were recorded for statistical analysis and bear out the clinical impression. More difficult to define in measurable terms is the symptom complex shown in each individual kindred. The clearest way to record this difference is to record aberrant patterns and to discuss their family aggregation.

Perhaps the most unusual family in this regard was the K family, a large kindred centred at present in Townsville, but with representatives all over Eastern Australia. A member of this family has been reported previously (Tyrer, 1957) in a discussion of the differentiation of hysteria from organic disease. Tyrer's description of this man is of interest for he showed spasmodic torticollis, involuntary clonic movements of the left lower part of the face and aphonia at the age of 22 years having commenced to show symptoms at

the age of 20 years. He died in 1967 at the age of 32 years suffering from advanced Huntington's chorea. It was the opinion of this author that the aphonia was of a hysterical nature, but in this family there are at present living five other patients, four women and one man, two sisters, a niece and a second cousin of this case and her son in whom the first evidence of the onset of the disorder has been the onset in late teens and early 20s of aphonia with exactly the same 'hysterical' features noted by Tyrer: inability to converse except in a whisper with phonation on coughing, but able to speak under the influence of strong emotion or, in the case of the man, to sing under the influence of alcohol. This family is also notable for the early age at onset of the disorder, the lengthy duration of the disease in some of the cases (40 years in one man) and the retention of a reasonable degree of intellect despite an appearance of gross dementia with chorea, hypertonia, mask-like facies, drooling salivation, and the aphonia described above. These features are sufficient to classify these patients as suffering from the Westphal variant of Huntington's chorea, though with rather less rigidity and dementia and rather more chorea than is usually seen in this form. All four living affected members and the case reported by Tyrer were of this type. Family descriptions suggest that other deceased members of this family may have presented a more typical picture of Huntington's disease, but the fact remains that these four cases were the only patients in the Queensland study to present with this picture, though others were seen presenting aphonia, akinesia, rigidity as late and terminal complications of the disorder.

Another family in which the disease had run a very similar course through several collateral lines was the E family. This family has previously been described by Parker (1958) and to it belonged the identical twins with the history of incendiarism and paranoid traits described by him. The disease in this family is late in onset, slow in progression, associated with little intellectual impairment but accompanied by considerable personality disturbance, the males in particular frequently showing aggressive psychopathic behaviour. The neurological features of the disease are those of typical Huntington's chorea. No patient has been diagnosed as suffering from the disease in this family below 35 years of age and one old lady was examined once at 72 and considered normal and again at 74 years when she showed obvious mild evidence of the disease. No one has died from the disease below 66 years of age, but one choreic succumbed to carcinoma at the age of 41 years. This family has remained reasonably highly placed on the social scale. Its members are for the most part well-to-do landholders and some are wealthy. Perhaps this is due to cultural inheritance, but, on the other hand, the late onset of the disorder does make maintenance of the integrity of the family less of a problem than in some other kindreds.

In distinction to these two families who represent opposite extremes of the condition, there is the more typical family represented by the A kindred. This pedigree is descended from a Maltese kindred, three representatives of which migrated to Australia and all three subsequently died of Huntington's chorea. There have been no unusual features among the 11 choreics from four sibships in this family. The average age at onset is 31·0 years. There is clinically very gross chorea, gross dementia, and gross emotional disturbance with the characteristic extraordinarily selfish egocentric personality of the typical Huntington's choreic. In three sibships different cultural influences have operated. One has sunk low on the social scale, its choreic members having come in contact with the police through drunkenness and violent behaviour. One sibship has been brought up in the confines of a strict and small religious sect, its affected male member having been a missionary in India, but he now has a record of violent behaviour to his wife and is institutionalized because of this. The third sibship grew up in a lower middle class environment, its affected male member having a record of petty delinquency and juvenile brushes with police and other authority. The pattern of behaviour is very similar, though the cultural background has varied widely in this kindred.

These are merely examples of recorded clinical impressions. Darwin is quoted as saying 'I have no faith in anything but measurement and the rule of three'. We now proceed to attempt a demonstration of statistically significant findings that suggest that there is a basic variation of types of Huntington's chorea.

TABLE 2

MEAN AGE AT ONSET OF HUNTINGTON'S CHOREA FOR MALES AND FEMALES OF 12 FAMILIES

	Family code											
	K	*F*	*A*	*M*	*G*	*O*	*H*	*N*	*D*	*I*	*E*	*L*
Males	20·0	32·3	30·5	26·5	44·0	31·7	35·8	47·0	44·0	46·8	45·6	52·0
Females	36·4	29·0	31·8	36·0	30·3	38·0	54·0	40·0	45·0	48·0	54·8	55·0
Total	30·5	30·6	31·0	33·3	35·8	35·9	39·4	43·5	44·6	47·3	49·9	53·5
n_M	4	4	6	2	2	3	8	2	5	4	7	2
n_F	7	4	4	5	3	6	2	2	3	3	6	2
n_{Tot}	11	8	10	7	5	9	10	4	8	7	13	4

ANALYSIS OF DATA

Table 2 shows mean age at onset, for males and females separately, over 12 families (not less than two cases per sex per family). A two-way analysis of variance (sex and families) was then carried out, treating families[2] as a random effect. The results are summarized in Table 3a. A similar analysis on duration of the disease produced no significant results (see Table 3b).

TABLE 3a

ANALYSIS OF VARIANCE* OF AGES AT ONSET OF HUNTINGTON'S CHOREA FOR MALES AND FEMALES (SEX) IN 15 FAMILIES (FAM.)

Source	*SS*	*d.f.*	*MS*	*F*
Fam.	5556·13	11	505·10	6·550†
Sex	207·36	1	207·36	2·689§
Fam. × sex	1810·96	11	164·63	2·135‡
Error	5552·54	72	77·12	
Total	13126·99	95		

* Because of fairly large inequalities between within-groups n's, Bartlett's test was applied, yielding a $\chi^2 = 18{\cdot}24$ for 19 d.f. with associated $P \doteqdot 0{\cdot}5$, and the hypothesis of homogeneity of within-groups variance was not rejected.
† Significant at 0·001. ‡ Significant at 0·05. § NS.

In the light of the significant 'families' F in Table 3a a further analysis was carried out. If families are separated into two blocks, those with means above the grand mean (38·99 years) and those with means below, there appears to be: (1) some variation between family means within each block (see Table 2); and (2) except for families H and K, no marked overlap between

[2] If families are treated as a fixed effect, the F for sex is still not significant at $\alpha = 0{\cdot}05$.

TABLE 3b

ANALYSIS OF VARIANCE OF DURATION OF HUNTINGTON'S CHOREA

Source	*SS*	*d.f.*	*MS*	*F**
1. Fam. groups	87·80	1	87·80	1·308
2. Sex	1·19	1	1·19	< 1
3. Sex × (fam. groups)	37·96	1	37·96	< 1
4. Error	3693·17	55	67·15	
5. Total	3820·31	58		

* No significant F.

blocks (see Figure). It was therefore decided to partition the sums of squares between families into two components, a sum of squares between family blocks as defined above and a sum of squares between families within the blocks, to test the hypothesis that differences between family means could be mainly accounted for by block differences with insignificant inter-family differences within blocks. The re-analysis thus has fixed factors, sex[3] and family group and a random effect, family, nested under family group. The paradigm for such an analysis can be found in Winer (1962) and the results are set out in Table 4a. Tests of the components involving the random factor (components (4) and (5)) at the 0·1 level (Winer, 1962) yielded non-significant Fs in both cases. Components (4), (5), and (6) were then pooled to obtain a revised estimate of error (Table 4b). It is arguable that the second analysis leads to a more parsimonious interpretation of the data than does the first but validation of the arbitrary classification into 'early-onset' (A_1) and 'late-onset' (A_2) blocks, by reference to additional data, seemed necessary. Such data,

[3] Retained because of the significant sex × family interaction (Table 3a).

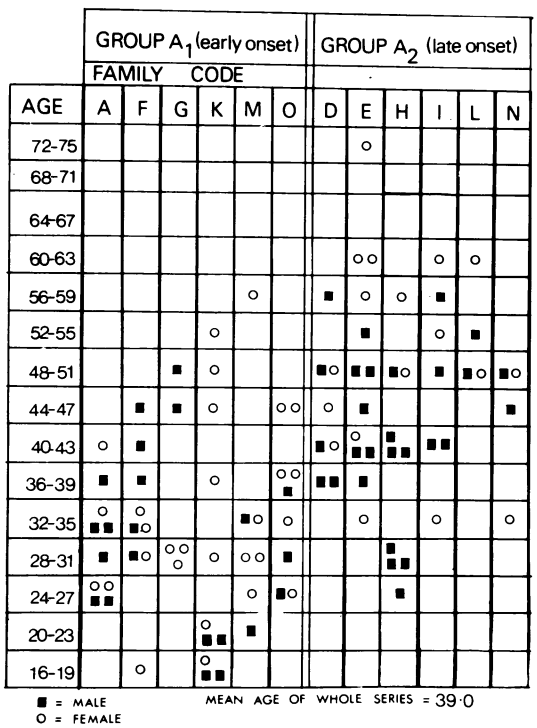

FIGURE. *Age grouping of early onset and late onset cases. ■ = male, ○ = female. Mean age of whole series = 39·0 years.*

TABLE 4a

REANALYSIS OF AGE-AT-ONSET DATA (STAGE 1)

Source		*SS*	*d.f.*	*MS*	*F*
1. Fam. groups		4392·32	1	4392·32	
2. Fam. w. groups		1163·81	10	116·38	1·51*
1.+2.	5556·13				
3. Sex		207·36	1	207·36	
4. Sex × (fam. groups)		584·26	1	584·26	
5. Sex × (fam. w. groups)		1226·70	10	122·67	1·59
4.+5.	1810·96				
6. Error		5552·54	72	77·12	
7. Total		13126·99	95		

*NS at $\alpha = 0{\cdot}1$.

TABLE 4b

REANALYSIS OF AGE-AT-ONSET DATA (STAGE 2)

Source	*SS*	*d.f.*	*MS*	*F*
1. Fam. groups	4392·32	1	4392·32	50·87*
2. Sex	207·36	1	207·36	2·40‡
3. Sex × (fam. groups)	584·26	1	584·26	6·77†
4. Error (pooled)	7943·05	92	86·34	
5. Total	13126·99	95		

* Significant at 0·001.
† Significant at 0·05.
‡ NS.

in the form of families which did not meet the criterion of at least two members of each sex were available. Table 5a shows ages by family and sex, family means and family classification as A_1 or A_2—that is, above or below the grand mean (38·99 years) of the original data. Table 5b shows the number of individuals who are 'correctly' and 'incorrectly' classified—that is, where ages were or were not within the age-range of the block to which their family mean was allocated.

Finally an analysis of variance, in the paradigm of the analysis summarized in Table 4b, was carried out on ages at death and the results are summarized in Table 6.

TABLE 5a

AGE AT ONSET—ADDITIONAL DATA

	Family code											
	B	*C*	*P*	*Q*	*R*	*S*	*T*	*U*	*V*	*W*	*X*	*Y*
Males	26, 35, 35, 35, 40, 50,	27 38	31 33	41		45	39 50	32 60			31 42	
Females	32	27		45	44, 49, 62	40			32 40	13 29		49 52
Family mean	36·1	30·7	32·0	43·0	51·7	42·5	44·5	46·0	36·0	21·0	36·5	50·5
Onset group	A_1	A_1	A_1	A_2	A_2	A_2	A_2	A_2	A_1	A_1	A_1	A_2

TABLE 5b

AGE AT ONSET—ADDITIONAL DATA (SEXES COMBINED)

	Family code												Total†
	B	*C*	*P*	*Q*	*R*	*S*	*T*	*U*	*V*	*W*	*X*	*Y*	
No. correct	5	3	2	2	3	2	2	1	1	2	1	2	26
No. incorrect	2	0	0	0	0	0	0	1	1	0	1	0	5

* 'Correct' and 'incorrect' classifications—that is, individuals within and without family classification range.
† χ^2 on totals (corrected for continuity) = 12·9 for 1 d.f.; $P < 0{\cdot}001$.

TABLE 6

ANALYSIS OF VARIANCE OF AGES AT DEATH OF HUNTINGTON'S CHOREA CASES

Source	*SS*	*d.f.*	*MS*	*F*
1. Fam. groups	1873·84	1	1873·34	16·63*
2. Sex	681·04	1	681·04	6·05†
3. Sex × (fam. groups)	80·82	1	80·82	< 1
4. Error	8450·50	75	112·67	
5. Total	11085·56	78		

* Significant at 0·001.
† Significant at 0·05.

DISCUSSION OF ANALYSES It seems to have been demonstrated, beyond reasonable doubt, that inter-family differences in the onset age of Huntington's chorea significantly exceed intra-family differences, and sex differences are not uniform across families. More parsimoniously, it seems possible that a hypothesis of at least two major genetically-differentiated groupings is tenable. This hypothesis receives some support from an analysis of data which are independent of the data generating the hypothesis.

No evidence was found of significant differences in duration of the disease. The pattern of ages at death is, in general, consistent with the foregoing findings. The inter-group significant difference is maintained. The change in the sex difference from non-significant at onset to significant at death is probably a reflection of the greater mean female longevity in the general population and the change in the sex × family interaction (significant at onset; non-significant at death) could be due to the increase in magnitude of the sex main-effect at death. The whole pattern seems to exhibit some coherence. It might be argued that the similarities noted above are due to the effects of a common environment within sibships, and not a reflection of an underlying genetic difference. For this reason, a comparison of the correlations between sib-sib pairs, parent-child pairs, and cousin-cousin pairs was made. The results are set out in Table 7. It can be seen that, where comparison is possible, the correlations are all strongly positive except in the case of duration in parent-child pairs. In this instance the observational errors associated with the spurious entity known as anticipation (Penrose, 1948) are conceivably responsible. Though not suitable for strict significance testing, these findings strongly suggest that the similarities are due to genetic variation and not environmental similarities. Moreover, the lack of falling off in the cousin-cousin pair correlation suggests that it is the major gene which varies from family to family, and not the effect of a common genetic background influencing the action of the Huntington's allele.

TABLE 7

INTRACLASS* CORRELATIONS† WITHIN THREE RELATIONSHIP GROUPS OVER ONSET-AGE, DEATH-AGE, AND DURATION

	Sib-sib	*Parent-child*	*Cousin-cousin*
Onset	+53 (100 pairs)	+44 (60 pairs)	+44 (97 pairs)
Death	+51 (51 pairs)	+59 (41 pairs)	‡
Duration	+77 (30 pairs)	−27 (20 pairs)	‡

* Since families with different n's are aggregated, these are not intraclass correlations in the strict sense (Fisher, 1946). No significance test can therefore be made.
† Decimal points omitted.
‡ Insufficient data.

DISCUSSION

It can be accepted on the basis of the findings presented here that the pattern of disease seen in Huntington's chorea runs in families, so that the differences between individuals within pedigrees are less than the differences between pedigrees. This finding is not new. Reed and Chandler (1959) with their somewhat larger data

analysed the differences in age of onset, at death, and in duration between sibships between kindreds and within kindreds and found that the similarity was greatest within a sibship, rather less between members of one kindred, and least between unrelated cases. They interpreted this as evidence in favour of a single Huntington's chorea gene acting against a background of common genes in the same family. Familial similarities in expression of Huntington's chorea have been examined by other workers. Fieller and Smith (1951) found positive correlations between siblings for ages at onset and death. Bell (1948) using material from published data found a high sib-sib correlation, and as long ago as 1899 Beeton and Pearson found a significant correlation of 0·26 between brothers in age at death.

The difficulty is to decide whether this is due to variations in the different Huntington's chorea alleles, or due to similarities in the genetic background within families. We interpret our evidence as supporting the hypothesis of variable alleles, though it is probable that a common genetic background and a common environment within sibships play a part. Indeed, the data from Reed and Chandler's study show that siblings suffering from the condition resemble one another more than do relatives within a kindred, though the differences are not significant. Though we know of no environmental influence which has any bearing on the time of onset or the rate of progression of Huntington's chorea, it would *a priori* be expected that such influences do exist, and the same is true for the influence of the total genotype. However, the clinical similarities between the symptom complex of the disorder in widely separated segments of a single kindred, and the quite startling differences between the expression of the disease in different families, makes the clinician incline to the opinion that different Huntington's chorea alleles are effecting this difference. This opinion receives support from the statistical analysis presented, which shows, not only that there is a significantly greater difference in at least one variable—namely, age at onset—between families than within families, but suggests that there are at least two separate forms of the disorder distinguished by relatively early and relatively late onset.

In the present state of knowledge concerning Huntington's chorea, where there is no understanding of the biochemical abnormality underlying the condition it is perhaps unwise to speculate in regard to its nature, but the genetic knowledge concerning the disorder allows certain tentative conclusions to be drawn. The mode of inheritance is that of a classical mendelian dominant. Although a minor structural rearrangement of chromosomal material such as a small deletion, duplication, or translocation could be responsible, it is more probable that the disease represents a point mutation in a structural or control gene. If this is so then it might be expected to behave in a similar manner to similar point mutations, with a recurrence rate of approximately one per 10^5 gametes, and as each structural locus or control locus represents a DNA segment of perhaps 10^3 base pairs, change in any pair of which might cause a disease of Huntington's type to appear, it is to be expected that these varying mutations would differ in their phenotypic effects one from another while breeding true in the same family. Less likely, in view of the conspicuous isolation of Huntington's chorea from all other genetically determined degenerative disorders of the nervous system, is the possibility that mutant alleles at different loci are responsible for the variant diseases in different families, in a manner analogous to the two loci responsible for ovalocytosis (Morton, 1956).

Myrianthopoulos (1966) recognized three separate clinical forms of the disease: the general case of Huntington's chorea, the rigid and akinetic form, and the childhood form of the disease. These correspond to Bruyn's adult type, Westphal variant, and juvenile types. We have not recorded a case of the childhood type. There have been several children of choreics who suffered from epilepsy, but on each occasion when the child was examined no evidence to suggest Huntington's chorea was detected. These juvenile cases have been reported to occur sporadically among families with the typical adult form of the disease. Without personal experience of such cases we cannot comment upon their significance, except to suggest that the complete absence of any records of such cases among nearly 300 well-documented cases from the Queensland kindreds either suggests that this form is very rare or that among the 47 Queens-

land kindreds there is no representative of the particular Huntington's chorea allele that is capable of giving rise to this syndrome. As recorded, we have encountered five living examples of the Westphal variant of the disorder and obtained the records of a sixth and seventh. We consider it suggestive that all seven of these are representatives of a single kindred that is aberrant in other ways. We consider that this particular form of Huntington's chorea is, on the evidence available, more probably the result of a separate mutant allele than the result of a predisposing background of common genes within this family.

REFERENCES

Beeton, M., and Pearson, K. (1899). Data for the problem of evolution in man. II. A first study of the inheritance of longevity and the selective death-rate in man. *Proceedings of the Royal Society*, **65**, 290–305.

Bell, J. (1948). Huntington's chorea, pp. 1–67. In *Nervous Diseases and Muscular Dystrophies. The Treasury of Human Inheritance*. Vol. IV. Cambridge University Press: London.

Bittenbender, J. B., and Quadfasel, F. A. (1962). Rigid and akinetic forms of Huntington's chorea. *Archives of Neurology* (Chicago), **7**, 275–288.

Brothers, C. R. D. (1949). The history and incidence of Huntington's chorea in Tasmania. *Proceedings of the Royal Australasian College of Physicians*, **4**, 48–50.

Bruyn, G. W. (1968). Huntington's chorea. Historical, clinical and laboratory synopsis, pp. 298–378. In *Handbook of Clinical Neurology*. Vol. 6. *Diseases of the Basal Ganglia*. Edited by P. J. Vincken and G. W. Bruyn. North-Holland: Amsterdam.

Chandler, J. H., Reed, T. E., and DeJong, R. N. (1960). Huntington's chorea in Michigan. III. Clinical observations. *Neurology* (Minneap.), **10**, 148–153.

Davenport, C. B., and Muncey, E. B. (1916). Huntington's chorea in relation to heredity and eugenics. *American Journal of Insanity*, **73**, 195–222.

Fieller, E. C., and Smith, C. A. B. (1951). Note on the analysis of variance and intraclass correlation. *Annals of Eugenics*, **16**, 97–104.

Fisher, R. A. (1946). *Statistical Methods for Research Workers*. 10th edn. Oliver and Boyd: Edinburgh.

McKusick, V. A. (1971). *Mendelian Inheritance in Man*. 3rd edn. Johns Hopkins Press: Baltimore.

Morton, N. E. (1956). The detection and estimation of linkage between the genes for elliptocytosis and the Rh blood type. *American Journal of Human Genetics*, **8**, 80–96.

Müller-Küppers, M., and Stenzel, K. (1963). Zum Problem der Frühmanifestation der Erbchorea. *Acta Paedopsychiatrica*, **30**, 348–355.

Myrianthopoulos, N. C. (1966). Huntington's chorea. *Journal of Medical Genetics*, **3**, 298–314.

Parker, N. (1958). Observations on Huntington's chorea based on a Queensland survey. *Medical Journal of Australia*, **1**, 351–359.

Penrose, L. S. (1948). The problem of anticipation in pedigrees of dystrophia myotonica. *Annals of Eugenics*, **14**, 125–132.

Reed, T. E., and Chandler, J. H. (1958). Huntington's chorea in Michigan. I. Demography and genetics. *American Journal of Human Genetics*, **10**, 201–225.

Tyrer, J. H. (1957). The differentiation of hysteria from organic neurological disease. *Medical Journal of Australia*, **1**, 566–571.

Winer, B. J. (1962). *Statistical Principles in Experimental Design*. McGraw-Hill: New York.

APPENDIX

In drawing up this appendix an effort has been made to codify as much information as possible in the smallest possible amount of space. The result may be a little confusing but the numbers specify the following rough estimates. Movement: 0 = no abnormal movement, 1 = minimal chorea, 2 = moderate chorea, 3 = marked chorea. Dementia, marital disturbance, anger outbursts, alcoholism, and sexual aberration are coded along similar lines. Psychiatric disturbance uses a finer grading from 0, which indicates no detectable disturbance, to 9, which indicates a state equivalent to raving lunacy. In 'Age at death' column, L denotes 'living'. Inst. in the column 'Ever in mental hospital' refers to placement in nursing home or similar custodial accommodation. The appendix contains all data from which the statistical analysis was made. It does not include the many ancestral cases for whom no accurate data were available. The pedigree number is that of the catalogue of genetic defects at Queensland Institute of Medical Research, which includes disorders other than Huntington's chorea.

APPENDIX TABLE

DETAILS OF PATIENTS

Pedigree no.	*Case*	*Sex*	*Movement*	*Dementia*	*Psychiatric disturbance*	*Social state (including no. of marriages)*	*Marital disturbance*	*Police record*	*Anger outbursts*	*Alcoholism*	*Sexual aberration*	*Age at onset (yr)*	*Age at death (yr)*	*Occupation or husband's*	*Ever in mental hospital*
12	II_2 Sib	M										38	54		
12	II_4 Sib	M	3	3	9	1	1	0	3	—	—		43	Labourer	Inst.
12	III_2	M	2	3	9	0	—	+	3	—	—	25	L	Labourer	Yes
12	III_3	F	2	3	—	0	—	0	—	0	—	35	L	Nil	Yes
12	III_6	M	3	3	—	1	—	—	3	3	—	25	36	Meat worker	
12	Sib III_7	M	3	3	9	0	—	+	3	3	3	33	L	Labourer	Yes
12	III_8	M	3	1	7	0	—	—	3	3	—	30	L	Meat worker	No
12	III_9	F	—	—	—	1	1	+	3	—	—	27	L	Wharfie	No
12	III_{13}	F	3	3	6	1	0	—	1	0	0	25	L	Reg. army	Inst.
12	Sib III_{17}	F	0	3	—	1	0	0	0	0	0	40	L	Shopkeeper	Yes
12	III_{23}	M	1	1	9	1	2	0	3	0	0	32	L	Missionary	Yes
13	III_3	M	3	3	3	1	0	0	—	3	0	40	53	Estate agent	Yes
13	Sib III_7	M	3	3	3	1	0	0	—	—	—	40	52	Baker	No
13	III_9	F	3	3	3	1	1	0	1	0	0	32	42	Storekeeper	Yes
13	III_4	M	2	0	0	1	0	0	0	0	0	50	L	Telephone worker	No
13	Sib III_6	M	3	3	6	0	0	0	3	3	0	35	47	Real estate agent	Yes
13	III_7	M	3	3	9	1	1	0	3	0	—	26	43	Dairy inspector	Yes
13	III_9	F	2	1	0	1	0	0	—	0	0	32	L	Bank clerk	No
13	III_{20}	M	1	0	6	0	0	+	—	3	—	35	L	A.L.P. secretary	No
13	III_{23}	M	1	0	0	1	0	0	—	—	—	35	L	Shearer	No
14	II_1	M	3	3	9	1	—	—	3	—	—	32	45		Yes
14	III_1	M	3	3	9	1	1	—	3	0	0	—	58	Chemist	Yes
15	III_2	M	3	3	9	1	3	+	3	0	1	42	L	Miner	Yes
16	Sib IV_1	M	3	3	9	1	3	0	3	3	—	38	53	Newspaper reporter	Yes
16	IV_5	M	3	3	9	1	3	0	3	3	—	27	50	Lieutenant	Yes
16	IV_4	F	3	3	9	1	1	+	3	—	—		?		Yes
16	IV_9	F	3	3	9	1	0	0	1	0	2	27	L	Artisan	Yes
19	II_2	M	—	—	—	—	—	—	—	—	—	48	—	—	Yes
19	III_4	F		3	9	1	1	—	3	0	0	50	58	Labourer	Yes
19	III_{10}	F	3	2	3	1	0	0	3	0	0	40	54	Labourer	No
19	Sib III_{12}	F	3	2	3	1	3	+	3	3	3		48	SP bookie	No
19	III_{14}	M	1	0	0	1	0	0	0	0	0	57	L	Meat worker	No
19	III_{18}	M	2	3	6	1	0	0	0	0	0	40	53	—	
19	IV_2	F	2	1	3	2	3	—	—	0	1	45	L		
19	Sib IV_{45}	M	0	0	6	1	3	—	3	3	0	39	L	Wharfie	No
19	IV_{47}	M	1	0	0	1	2	—	3	3	0	38	L	Process worker	No
22	III_2	F	3	1	0	1	0	0	0	0	0	55	73	Officer, fire brigade	No
22	III_{15}	M	3	3	9	1	3	0	3	0	0	60	> 72	Sailmaker	No
23	III_4	F	3	0	3	1	1	0	3	0	0	57	66	Farmer	Inst. No
23	IV_1	F	3	0	3	1	1	0	2	0	0	62	85	Farmer	No
23	IV_6	M	3	3	9	1	3	+	0	0	0	42	66	Successful timber merchant	Yes
23	Sib IV_8	M	3	3	9	1	2	0	3	0	0	42	66	Share farmer	Yes
23	IV_{13}	F	3	3	9	1	1	+	3	0	0	61	76		Yes
23	IV_{15}	F	1	0	0	1	0	0	0	0	0	74	L	Farmer	No
23	V_1	M	1	1	0	1	0	0	0	0	0	53	L	Telephone lineman	No
23	Sib V_3	M	3	1	0	1	0	0	0	0	0	51	L		No
23	V_5	M	3	2	0	1	0	0	0	0	0	50	L	Farmer	No
23	V_{34}	M	2	2	6	1	3	0	3	3	0	45	L	Farmer	Yes
23	Sib V_{36}	F	2	0	0	1	3	0	0	0	0	40	41	Trained nurse	No
23	V_{38}	M	1	0	1	1	0	0	1	0	0	36	L	Railwayman	No
23	V_{46}	F	3	2	3	1	0	0	2	1	0	35	L	Farmer	Yes
24	III_5	M	2	1	0	1	3	0	3	0	0	45	L	Company manager	No
26	III_2	F				1							56	Grazier	No
26	II_2	M	3	—	—	1	0	0	—	—	—	—	54	Grazier	No
26	Sib II_{10}	M				1							63		No
26	II_{11}	F				1							63		Inst. No
26	II_{13}	F				1							72		No
26	III_3	F	3	3	6	1	3	0	2			35	42	Garage proprietor	Yes
26	Sib III_6	F				1						34	46	Grazier	Yes
26	III_8	M				1						34	44	Farm hand	Yes

Appendix Table continued

Pedigree no.	Case	Sex	Movement	Dementia	Psychiatric disturbance	Social state (including no. of marriages)	Marital disturbance	Police record	Anger outbursts	Alcoholism	Sexual aberration	Age at onset (yr)	Age at death (yr)	Occupation or husband's	Ever in mental hospital
26	Sib III_9	M	3	3	6	1	0	0	0	0	0	31	>47 Still L	Farm hand	No
26	Sib III_{19}	M	3	0	0	1	0	+	0	0	0		41	Grazier	No
26	Sib III_{24}	M	1	1	9	1	3	+	3	3	0	37	L	Grazier	No
26	IV_3	F	2	0	0	1	0	0	0	0	0	30	L	Executive	No
26	IV_5	M	1	1	6	0	0	+	—	—	+3	27	L	Fitter and turner	No
26	IV_6	F	1	0	3	0	0	0	3	—	1	17	L	Invalid	No
27	II_3	M	3	—	9	1			3				62	—	No
27	Sib III_3	M	—	—	9	1	—	—	—	3	—	—	59	—	No Inst.
27	Sib III_5	F	1	3	9	1	3	+	3	3	3		50	Car salesman	Yes
33	III_2	M	3	1	3	1	2	0	3	0	0	33	>60 Still L	Mechanic	No
33	III_3	M	3	1	3	1	3	+							No
33	III_7	M	3	1	3	1	3	+	3	0	0	31	42	Painter	No
35	Sib III_5	M	3	2	3	0	0	0	1	0	0	41	>52 L	Qld. Champion weight lifter	No
35	Sib III_9	F	2	2	0	1	0	0	0	0	0	45	48 L	Office worker	No
36	II_5	M	3	3	9	1	2	++	3	0	1	47	62	Company manager	Yes
37	I_1	M	3	3	0						—		72	Timber manager	No
37	Sib II_2	M	3	3	0	1		0	1	0	0	45	70	Farmer	No
37	Sib II_3	F	3	3	0	1	3		1		—	30	56	Farmer	No
37	Sib III_{10}	M	3	0	0	1	0	0	0	0	0	43	L	Farmer	No
37	Sib III_{17}	F	3	3	3	1	1	0	0	0	0	31	L	Mechanic	No
37	IV_5	F	3	0	0	0	0	0	0	0	0	30	L	Switchboard operator	No
39	IV_1	M	3	3	6	1	—	—	—	—	—		60		No
39	IV_3	F	3	3	9	1	1	—	3	—	0	—	L	Mechanic	No
39	IV_5	M	3	3	6	0	0	—	—	—	0	—			No
39	V_3	M	1	0	0	1	—	0	1	0	0	31	L	Truck driver	No
42	II_4	F	3	3	6	1	0	0	3	0	0	62	73	Dairy farmer	No
42	Sib III_3	F	3	3	6	1	0	0	2	0	0	44	L	Motor accessories firm	No Inst.
42	Sib III_5	F	1	0	0	1	0	+	0	0	0	49	L	Postman	
44	I_1	M											70's	Farmer	No
44	Sib II_6	F	3	1	0	1	0	0	3	0	0		70's	Farmer	No
44	Sib II_8	F	3	1	—	1	0	0	—	0	0		>80 L		No
44	II_{10}	M	3	3	9	1	3	0	3	0	0	40	58	Labourer	Yes
44	III_{16}	M	3	2	6	1	2	0	3	0	0		>65 L	—	No
44	Sib III_{18}	F	3	2	6	2	3	0	2	0	0	52	>62 L	Labourer	No
44	Sib III_{20}	F											59	—	No
44	III_{24}	M	2	0	0	0	0	—	—	—	—	40	L	Railwayman	No
44	Sib III_{33}	F	2	0	—	2	—	—	—	—	—	60	L	Farmer	No
44	Sib III_{35}	M	2	0	—	0						57	L	Farmer	No
44	III_{40}	M	1	0	6	0	0	0	3	0	0	50	L	Builder's labourer	No
44	Sib III_{42}	F	1	0	3	2	3	0	—	—	—	32	>47 L	Meat worker	No
45	II_2	M	—	—	—	1						45	69	Grazier	No Inst.
45	III_8	F	1	1	0	1	3	+	2	0	0	40	L	Waitress	No
46	I_2	F	—	—	—	—	—	—	—	—	—	—	57		
46	Sib II_2	F	—	—	—	—	—	—	—	—	—	—	62		No
46	Sib II_8	F	—	—	—	—	—	—	—	—	—	—	76	—	No
46	Sib II_{11}	F	—	—	—	—	—	—	—	—	—	—	72	—	No
47	II_2	F	3	3	3	1	0	0	2	0	0	—	c64	Miner	No Inst.
47	III_5	M	3	0	9	—	—	+	—	—	—	—	40		No
47	III_7	M	3	3	9	1	2	—	3	—	1	41	58	Mill worker	No
47	III_{15}	M	3	3	6	0	0	—	3	—	—	27	41	Bore worker	Yes
47	Sib III_{17}	F	3	1	0	1	0	0	2	0	0	51	71	Executive	No Inst.
47	III_{20}	M	3	0	0	1	0	0	2	0	0	40	66	Motor mechanic	No

Appendix Table continued

Pedigree no.	*Case*	*Sex*	*Movement*	*Dementia*	*Psychiatric disturbance*	*Social state (including no. of marriages)*	*Marital disturbance*	*Police record*	*Anger outbursts*	*Alcoholism*	*Sexual aberration*	*Age at onset (yr)*	*Age at death (yr)*	*Occupation or husband's*	*Ever in mental hospital*
47	III_{18}	M	3	3	6	1	2	—	3	3	—	40	61	Wharf labourer	No
47	Sib IV_3	M	2	1	8	1	3	+	3	3	0	30	> 57 L	Shop manager	Yes
47	Sib IV_6	F	1	1	6	1	—	0	3	—	—	57	L	Company manager	No
47	Sib IV_{13}	M	3	3	6	1	0	+	3	0	0	28	58	Timber works owner	Yes
47	Sib IV_{15}	M	3	3	6	1	0	0	0	0	0	31	53	Timber worker	No
47	Sib IV_{18}	F											c57	Owner of motor garage	No
47	IV_{24}	M	1	1	0	1	1	0	2	0	0	49	L	Draughtsman	No
47	IV_{30}	F	1	0	3	1	0	—	—	—	0	46		Timber owner	No
47	V_9	F	1	0	0	1	0	—	0	0	0	30			
50	IV_3	F	3	1	1	1	0	0	1½	0	0	38	58	Builder	No Inst.
51	III_8	M	3	2	1	1	0	0	1	0	0	24	42	SGIO	No Inst.
53	II_9	F	3	1	0	1	0	0	0		1	50	73	Wharfie	No
53	Sib III_6	M	3	—	—	0	—	—	—	—	—	—	40	—	Yes
53	Sib III_8	M	3			0	—						58	—	No
53	III_{26}	F	3	1	0	1	—		—	—	—	55	73	Wharfie	No
53	III_{30}	F	3	2	0	1	0	0	0	0	0	45	59	Vaudeville	No
53	IV_5	F	1	1	0	1	2	0	0	0	0	36	L	Labourer	No
53	IV_{49}	M	3	1	0	1	3	—	—	—	0	23	62	Labourer	No
53	IV_{65}	F	3	1	0	1	3	+	0	—	3	21	L	Labourer	No
53	Sib IV_{65}	M	3	3	0	0	0	+	0	—	—	18	31	Theatre projector	No
53	Sib IV_{70}	F	2	1	2	1	2	+	0	0	0	29	L	Labourer	No
53	Sib IV_{71}	M	3	3	3	0	0	0	0	3	0	19	32	Labourer	Yes
53	V_5	M	0	0	0	0	0	0	0	1	0	20	L	Labourer	No
53	V_{78}	F	0	0	0	1	0	0	0	0	0	19	L	Labourer	No
55	III_5	M	3	3	9	1	3	+	3	3	1	40?	L	Anthropologist	No
78	II_2	M	3	0	0	1	0	0	1	0	0	50	76	Farmer	No
78	III_2	M	2	2	0	1	0	0	0	0	0	39	57	Farmer	No
80	I_1	F	3	3		1						46	64	Farmer	No Inst.
80	Sib II_2	M	3			1						50	64		
80	Sib II_5	F	1	0	0	1	0					60	L	—	No
80	Sib II_7	F	3	2	6	1	0	0	3	—	—	50	L	—	No
80	Sib II_9	M	1	0	0	1	0	0				54	L	Farmer	No
81	II_5	M	3	1	9	0	0	+	3	—	0	32	L	Labourer	Yes
82	I_1	M	3	3	—	—	—	—	—	0	—	—	—	Wheelwright	No Inst.
82	Sib II_2	F	3	3	6	1	0	—	3	0	0	30	58	Miner	No.
82	Sib II_4	F	—	—	—	—	—	—	—	—	—	50	76	—	No Inst.
82	Sib II_6	F	3	3	6	1	3	0	3+ +	0	0	35	65	Separated	Yes
82	Sib II_{11}	M	3	3	9	1	2	+	3	0	0			Moving from job to job	Yes
82	Sib III_1	M	3	3	9	1	3	0	3	2	0	20	58	Schoolmaster	No Inst.
82	Sib III_5	F	2	0	3	1	0	0	2	0	0	57	L	Builder	No
82	Sib III_7	F	3	3	9	0	—	0	3	0	1	27	L	None	Yes
82	IV_4	F	2	2	0	1	—	0	—	0	0	31	L		No
82	IV_5	M	1	0	3	1	—	0	—	0	0	33	L	Carpenter	No
83	II_1	M	3	3	9	1	2	+	3	0	0	c40	61	Clerk	No
84	I_3	F	3	3	3	2	0	0	0	0	1	32	73	Labourer	No
84	Sib II_1	M	3	3	9	1	3	+	3	3	+	48	61	Labourer	Yes
84	Sib II_6	M	3	0	0	1	0	0	0	0	0	46	50	Labourer	Yes
84	Sib II_8	F	1	0	6	2	3	0	1	3	3	48	L	Mill worker	No
87	II_8	F	3	3	9	1	1	0	1	0	0	c45	c68	Mill worker	No
87	III	F	2	2	5	1	3	0	—	—	3	—	> 64 L	Labourer	No
87	Sib III_{22}	F	3	2	9	2	3	0	3	0	1	38	L	Farmer	No
87	Sib III_{28}	F	3	3	9	2	3	0	3	0	1	27	55	Company manager	No
87	Sib III_{30}	M	3	3	9	1	3	0	3	3	3	37	L	Cane cutter	Yes
87	Sib III_{36}	F	3	3	3	1	2	0	1	0	2	35	L	Labourer	No

Appendix Table continued

Pedigree no.	Case	Sex	Movement	Dementia	Psychiatric disturbance	Social state (including no. of marriages)	Marital disturbance	Police record	Anger outbursts	Alcoholism	Sexual aberration	Age at onset (yr)	Age at death (yr)	Occupation or husband's	Ever in mental hospital
87	Sib {III_{44}	F	1	1	3	1	2	0	2	0	0	44	L	Truck driver class IV	No
87	IV_{14}	F	1	1	0	1	3	0	0	0	0	39	L	Labourer	No
87	IV_{18}	M	1	0	4	1	2	+	3	3	1	31	L	Labourer	No
87	IV_{38}	M	1	0	0	1	0	0	0	0	0	27	L	Truck driver	No
89	II_8	M	—	—	—	—	—	—	—	—	—	60	72		Yes
89	III_2	F	3	3	3	1	2	—	2	0	0	44	>60 L	Executive	No Inst.
90	II_8	M	3	0	0	1	0	0	2	0	0	55	>72 L		No Inst.
91	II_2	F	3	3	9	1	3	0	3	0	0	40	>52 L	Labourer	Yes
91	III_2	F	1	1	7	1	2	0	3	0	0	32	>34 L	Truck driver	No
92	II_9	F	3	0	0	1	3	0	0	0	1	29	49		No
92	III_9	F	3									13	33		
95	II_1	M	3	1	6	1	1	0	2	0	0	60	>67	Carpenter	No
95	III_3	F	1	0	3	1	3	0	2	0	0	32	L	Mechanic	No
101	II_{13}	F	3	1	0	1	3	0	0	0	0	32	L		No
107	II_3	F	3	3	3	1	1	0	2	0	0	52	53	Accountant	Yes
107	III_4	F	3	0	0	1	0	0	0	0	0	49	67	Cane cutter	No
113	II_3	F	3	2	6	1	—	—	—	—	—	45	L	Carpenter	No
117	II_1	M	3	3	9	1	3	0	3	2	0	42	61	School-teacher	Yes
117	III_2	M	3	1	9	1	3	0	3	3	0	31	>40 L	Sheet metal worker	Yes