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 re-

mains, 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 pre-senile 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 aponia 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 aponia 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, hypertonias, mask-like facies, drooling salivation, and the aponia 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 aponia, 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 suffer-

ing 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 families² 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 $\chi^2 = 18.24$ for 19 d.f. with associated $P \approx 0.5$, 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 $\alpha = 0.05$.

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, sex³ 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' (A₁) and 'late-onset' (A₂) blocks, by reference to additional data, seemed necessary. Such data,

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

AGE	GROUP A ₁ (early onset)						GROUP A ₂ (late onset)					
	FAMILY CODE											
	A	F	G	K	M	O	D	E	H	I	L	N
72-75								○				
68-71												
64-67												
60-63								○		○	○	
56-59					○		■	○	○	■		
52-55				○				■			○	■
48-51			■	○			■	○	■	○	■	○
44-47		■	■	○		○	○					■
40-43	○	■					■	○	■	■	■	
36-39	■	■		○		○	■	■				
32-35	○	○			■	○					○	○
28-31	■	○	○	○	○	■			■	■		
24-27	○	■			○	○			■			
20-23				○	■							
16-19		○		○	■							

■ = MALE
○ = FEMALE

MEAN AGE OF WHOLE SERIES = 39.0

FIGURE. Age grouping of early onset and late onset cases. ■ = male, ○ = female.
Mean age of whole series = 39.0 years.

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 A₁ or A₂—that is, above or below the grand mean (38.99 years) of the original data. Table 5b shows the number of individuals who are 'cor-

rectly' 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, 32	27 38	31 33	41		45	39 50	32 60			31 42	
Females		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 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 $\alpha = 0.1$.

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.

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.; $P < 0.001$.

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 $\times$ (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 $\times$ 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

TABLE 7
INTRACLASST* 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 intra-class correlations in the strict sense (Fisher, 1946). No significance test can therefore be made.

† Decimal points omitted.

‡ Insufficient data.

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.

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.

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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	M										38	54		
12	II ₄	M	3	3	9	1	1	0	3	—	—		43	Labourer	Inst.
12	II ₂	M	2	3	9	0	—	+	3	—	—	25	43	Labourer	Yes
12	III ₃	F	2	3	—	0	—	0	—	0	—	35	—	Nil	Yes
12	III ₆	M	3	3	—	1	—	—	3	3	—	25	36	Meat worker	
12	III ₇	M	3	3	9	0	—	+	3	3	3	33	—	Labourer	Yes
12	III ₈	M	3	1	7	0	—	—	3	3	—	30	—	Meat worker	No
12	III ₉	F	—	—	—	1	1	+	3	—	—	27	—	Wharfie	No
12	III ₁₃	F	3	3	6	1	0	—	1	0	0	25	—	Reg. army	Inst.
12	III ₁₇	F	0	3	—	1	0	0	0	0	0	40	—	Shopkeeper	Yes
12	III ₂₃	M	1	1	9	1	2	0	3	0	0	32	—	Missionary	Yes
13	II ₃	M	3	3	3	1	0	0	—	3	0	40	53	Estate agent	Yes
13	II 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	—	Telephone worker	No
13	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	—	Bank clerk	No
13	III ₂₀	M	1	0	6	0	0	+	—	3	—	35	—	A.L.P. secretary	No
13	III ₂₃	M	1	0	0	1	0	0	—	—	—	35	—	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	—	Miner	Yes
16	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	—	Artisan	Yes
19	II ₂	M	—	—	—	—	—	—	—	—	—	48	—		Yes
19	III ₄	F	3	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	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	—	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	—		
19	IV ₄₅	M	0	0	6	1	3	—	3	3	0	39	—	Wharfie	No
19	IV ₄₇	M	1	0	0	1	2	—	3	3	0	38	—	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	II ₄	F	3	0	3	1	1	0	3	0	0	57	66	Farmer	Inst.
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	No
23	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	—	Farmer	No
23	V ₁	M	1	1	0	1	0	0	0	0	0	53	—	Telephone lineman	No
23	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	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	II ₁₀	M				1						63	—		No
26	II ₁₁	F				1						63	—		Inst.
26	II ₁₃	F				1						72	—		No
26	III ₃	F	3	3	6	1	3	0	2			35	42	Garage proprietor	Yes
26	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	Farm hand	No	
26	Sib { III ₁₉	M	3	0	0	1	0	+	0	0	0	41	Still L	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	—	—	—	—	—	—	62	—	—	No
27	Sib { III ₃	M	—	—	9	1	—	—	—	3	—	—	59	—	—	No
27	Sib { III ₅	F	1	3	9	1	3	+	3	3	3	—	50	Car salesman	Inst.	
33	III ₂	M	3	1	3	1	2	0	3	0	0	33	> 60	Mechanic	Yes	
33	III ₃	M	3	1	3	1	3	+	—	—	—	—	Still L	—	No	
33	III ₇	M	3	1	3	0	0	0	1	0	0	41	> 52	Painter	No	
35	Sib { III ₅	M	3	2	3	0	0	0	—	—	—	—	48 L	Qld. Champion weight lifter	No	
35	Sib { III ₉	F	2	2	0	1	0	0	0	0	0	45	62	Office worker	No	
36	II ₅	M	3	3	9	1	2	+	3	0	1	47	72	Company manager	Yes	
37	I ₁	M	3	3	0	0	—	—	—	—	—	—	70	Timber manager	No	
37	Sib { II ₂	M	3	3	0	1	3	0	1	0	0	45	56	Farmer	No	
37	Sib { II ₃	F	3	3	0	1	0	0	0	0	0	30	L	Farmer	No	
37	Sib { III ₁₀	M	3	0	0	1	0	0	0	0	0	43	L	Mechanic	No	
37	Sib { III ₁₇	F	3	3	3	1	1	0	0	0	0	31	L	Switchboard operator	No	
37	IV ₅	F	3	0	0	0	0	0	0	0	0	30	L	—	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	
42	Sib { III ₅	F	1	0	0	1	0	+	0	0	0	49	L	Postman	Inst.	
44	I ₁	M	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	—	70's	Farmer	No	
44	Sib { II ₈	F	3	1	—	1	0	0	—	0	0	—	> 80	—	No	
44	Sib { 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	—	No	
44	Sib { III ₁₈	F	3	2	6	2	3	0	2	0	0	52	> 62	Labourer	No	
44	Sib { III ₂₀	F	—	—	—	—	—	—	—	—	—	—	59	—	No	
44	Sib { 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	Sib { 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	Meat worker	No	
45	II ₂	M	—	—	—	1	—	—	—	—	—	45	69	Grazier	No	
45	Sib { III ₈	F	1	1	0	1	3	+	2	0	0	40	L	Waitress	Inst.	
46	I ₂	F	—	—	—	—	—	—	—	—	—	—	57	—	No	
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	
47	Sib { III ₅	M	3	0	9	—	—	+	—	—	—	—	40	—	Inst.	
47	Sib { III ₇	M	3	3	9	1	2	—	3	—	1	41	58	Mill worker	No	
47	Sib { 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	
47	III ₂₀	M	3	0	0	1	0	0	2	0	0	40	66	Motor mechanic	Inst.	

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	Sib { III ₁₈ IV ₃	M	3	3	6	1	2	—	3	3	—	40	61	Wharf labourer	No	
M		2	1	8	1	3	+	3	3	0	30	> 57	Shop manager	Yes		
F		1	1	6	1	—	0	3	—	—	57	L	Company manager	No		
47	Sib { IV ₆ IV ₁₃ IV ₁₅ IV ₁₈	M	3	3	6	1	0	+	3	0	0	28	58	Timber works owner	Yes	
M		3	3	6	1	0	+	0	0	0	31	53	Timber worker	No		
F											c57	Owner of motor garage	No			
M		1	1	0	1	1	0	2	0	0	49	L	Draughtsman	No		
47	IV ₂₄	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	
51	III ₈	M	3	2	1	1	0	0	1	0	0	24	42	SGIO	No	
53	Sib { II ₉ III ₆ III ₈ III ₂₆ III ₃₀ IV ₅ IV ₄₉ IV ₆₅ IV ₆₅ IV ₇₀ IV ₇₁ V ₅ V ₇₈ III ₅ II ₂ III ₂ I ₁	F	3	1	0	1	0	0	0	—	1	50	73	Wharfie	No	
M		3	—	—	0	—	—	—	—	—	—	—	40	—	—	Yes
M		3			0	0	—						58	—	—	No
F		3	1	0	1	—		—	—	—	—	55	73	Wharfie	No	
F		3	2	0	1	0	0	0	0	0	0	45	59	Vaudeville	No	
F		1	1	0	1	2	0	0	0	0	0	36	L	Labourer	No	
M		3	1	0	1	3	—	—	—	0	0	23	62	Labourer	No	
F		3	1	0	1	3	+	0	—	3	21	L	Labourer	No		
M		3	3	0	0	0	+	0	—	—	18	31	Theatre projector	No		
F		2	1	2	1	2	+	0	0	0	29	L	Labourer	No		
M		3	3	3	0	0	0	0	0	3	0	19	32	Labourer	Yes	
M		0	0	0	0	0	0	0	0	1	0	20	L	Labourer	No	
F		0	0	0	1	0	0	0	0	0	0	19	L	Labourer	No	
M		3	3	9	1	3	+	3	3	1	40?	L	Anthropologist	No		
M		3	0	0	1	0	0	1	0	0	0	50	76	Farmer	No	
M	2	2	0	1	0	0	0	0	0	0	39	57	Farmer	No		
F	3	3		1							46	64	Farmer	No		
80	Sib { II ₂ II ₅ II ₇ II ₉ II ₅ I ₁	M	3			1						50	64		Inst.	
F		1	0	0	1	0						60	L	—	No	
F		3	2	6	1	0	0	3	—	—	—	50	L	—	No	
M		1	0	0	1	0	0					54	L	Farmer	No	
M		3	1	9	0	0	+	3	—	0	32	L	Labourer	Yes		
M		3	3	—	—	—	—	—	0	—	—	—	—	Wheelwright	No	
82	Sib { II ₂ II ₄ II ₆ II ₁₁	F	3	3	6	1	0	—	3	0	0	30	58	Miner	Inst.	
F		—	—	—	—	—	—	—	—	—	—	50	76	—	No	
F		3	3	6	1	3	0	3+ +	0	0	35	65	Separated	Inst.		
M		3	3	9	1	2	+	3	0	0			Moving from job to job	Yes		
82	Sib { III ₁ III ₅ III ₇ IV ₄ IV ₅ II ₁ I ₃ II ₁ II ₆ II ₈ III	M	3	3	9	1	3	0	3	2	0	20	58	Schoolmaster	No	
F		2	0	3	1	0	0	2	0	0	57	L	Builder	Inst.		
F		3	3	9	0	—	0	3	0	1	27	L	None	No		
F		2	2	0	1	—	0	—	0	0	31	L		No		
M		1	0	3	1	—	0	—	0	0	33	L	Carpenter	No		
M		3	3	9	1	2	+	3	0	0	c40	61	Clerk	No		
F		3	3	3	2	0	0	0	0	1	32	73	Labourer	No		
M		3	3	9	1	3	+	3	3	+	48	61	Labourer	Yes		
M		3	0	0	1	0	0	0	0	0	46	50	Labourer	Yes		
F		1	0	6	2	3	0	1	3	3	48	L	Mill worker	No		
F		3	3	9	1	1	0	1	0	0	c45	c68	Mill worker	No		
F		2	2	5	1	3	0	—	—	3	—	> 64	L	Labourer	No	
87	Sib { III ₂₂ III ₂₈ III ₃₀ III ₃₆	F	3	2	9	2	3	0	3	0	1	38	L	Farmer	No	
F		3	3	9	2	3	0	3	0	1	27	55	Company manager	No		
M		3	3	9	1	3	0	3	3	3	37	L	Cane cutter	Yes		
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	Executive	No
													L		Inst.
90	II ₈	M	3	0	0	1	0	0	2	0	0	55	>72		No
													L		Inst.
91	II ₂	F	3	3	9	1	3	0	3	0	0	40	>52	Labourer	Yes
													L		
91	III ₂	F	1	1	7	1	2	0	3	0	0	32	>34	Truck driver	No
													L		
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	Sheet metal worker	Yes
													L		