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Review article

The epidemiology of Huntington's disease

Peter S. Harper

Institute of Medical Genetics, University of Wales College of Medicine, Heath Park, Cardiff, UK

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Summary. The available information on the world distribution of Huntington's disease (HD) from population surveys and death rate analysis is summarised and discussed in the light of genetic studies. It is concluded that most European populations, both Northern and Southern, show a relatively high prevalence (4–8 per 100,000), and that the disorder may also be frequent in India and parts of central Asia. HD is notably rare in Finland and in Japan, but data for Eastern Asia and Africa are inadequate. The disorder may have been underestimated in the American black population. Populations derived from recent European imigration show frequencies and origins of HD comparable to those expected from their own origins and expansion; there is no evidence to suggest that the HD gene has spread disproportionally and its selective effect may be close to neutral. Multiple separate introductions of the gene have been the rule in large populations. Several major foci of HD exist as the result of rapid population expansion. It is likely that a number of separate mutations for HD will be shown to be responsible for the disease, but that the high frequency of HD in European populations will prove to be the result of one or a very small number of mutations, probably of great antiquity.

Introduction

Huntington's Disease (HD) is one of the most important genetic disorders of adult life. Its severe and progressive physical and psychiatric effects on the central nervous system, its wide distribution and in many regions its considerable frequency, as well as the recent possibilities for molecular genetic prediction, all combine to give a high level of interest among clinical geneticists and basic scientists. Family and population data are available from many countries, but so far there have been few attempts to combine them to give a picture of the overall geographical distribution and epidemiology of the disorder. This article attempts to provide such an overview.

HD has long been recognised as following autosomal dominant inheritance, the essential features of this being recognized by Huntington himself in his original description in 1872 (Huntington 1872), while the specific inheritance pattern was documented as early as 1908 (Punnett 1908). Numerous detailed genetic analyses have since been carried out, especially in relation to factors influencing age at onset, gene penetrance and fitness. Conneally (1984) has provided a valuable review of this work and recent studies have been documented by the author (Harper 1991). The localisation of the gene on chromosome 4 (Gusella et al. 1983) and subsequent molecular analysis has made it likely that the HD gene itself will be identified and isolated in the very near future, giving the possibility of recognising specific mutations and tracing their origins. When this point is reached the data collected here should prove useful as a foundation for specific molecular studies of HD, even though they will require a complete reappraisal in the light of such developments.

Some apology is due for the title used here in view of the fact that the author is not an epidemiologist but a clinical geneticist. However, it should become clear from this review that the epidemiological study of a Mendelian disorder such as HD depends heavily on classical genetic approaches and analysis, while the more conventional epidemiological methods designed for commoner disorders with no clear inheritance pattern have limitations in the Mendelian situation.

Family studies and geographical distribution

Individual family studies of HD have been undertaken since the disorder was first recognised, while as early as 1916 Davenport and Muncey (1916) reported an extensive collection of data on families in the New England region of America. More systematic studies such as that by Julia Bell in Britain (Bell 1934) provided the foundations for detailed genetic analysis which remain valid today. However, such collections of data are of limited value epidemiologically since they do not reflect an attempt to obtain complete ascertainment of HD patients and families in a defined area. Fortunately a large number of thorough geographically based studies have been carried out in different areas, allowing a remarkably extensive, though not complete, picture to be obtained of the geographical distribution of HD. Before discussing these in detail, it is important to emphasise some of the criteria that a study of this type must fulfil if it is to be of general

epidemiological value, rather than of purely local interest.

1. The geographical area must be well defined (usually corresponding to some administrative or political boundary. The area must be sufficiently large to avoid bias from a particularly large kindred, but sufficiently small to allow complete coverage of all of it by the investigator (500,000–5,000,000 probably represent the outer limits for population size). All parts of the area should ideally be covered with equal thoroughness.

2. As many separate methods of ascertainment should be used as possible, e.g. general and psychiatric hospital records, letters to family doctors, neurologists and other clinicians, existing genetics records and death certificates. If multiple ascertainment is frequent, this is usually an indication that ascertainment is not going to be seriously deficient.

3. Intensive search for secondary cases is essential. In HD, more than most genetic disorders, all investigators are struck by the number of new affected patients discovered through a detailed and systematic family survey, often as the result of a home visit, whose existence was totally unsuspected, and who would not have been included in any survey limited to primary cases. The thoroughness of this aspect will probably be the largest single factor in determining prevalence.

4. Any study must be continued over a considerable period of time. Three years is probably a minimum and five preferable, but even then new families will be found in areas where one was confident that one had achieved total ascertainment. It is even better to repeat the survey after an interval; this usually produces a significant increase in prevalence.

5. A prevalence date should be chosen that is sufficiently remote (5–10 years) from the time of the study, to allow existing cases to be recognized and diagnosed but not to have died and been forgotten.

The author's original South Wales study (Walker et al. 1981) shows how this can be done. It was carried out over a period of almost 5 years (1973–1978), with a prevalence date of 25/26 April, 1971, corresponding to the decennial census. The area chosen (industrial South Wales) was compact, had well defined boundaries, and had a total population on the prevalence date of 1,720,901, giving a resulting prevalence estimate of 7.61 per 100,000. It should be noted that when re-analysed 10 years later, taking a prevalence date of 1981, the prevalence was found to be higher at 8.85 per 100,000 (Quarrell et al. 1988). Table 1 summarises some of the epidemiological aspects of the South Wales study.

Table 1. Prevalence estimates of Huntington's disease (HD) in South Wales

	Study	
	Walker et al. (1981)	Quarrell et al. (1988)
Prevalence date	April 1971	April 1981
Census population	1,720,000	1,728,000
No. of living affected	131	153
Prevalence (per 100,000)	7.61	8.85

Prevalence studies of HD in Europe

Europe is remarkable for the large number of detailed prevalence studies of HD that have been carried out in different countries, most of them fulfilling the criteria listed above, though all are likely to fall short of full ascertainment by a greater or lesser degree. Figure 1 and Table 2 show the distribution of studies known to the author, though it is possible that other unpublished data exist. Studies based on small areas likely to have been studied specifically because of their high frequency of HD have been omitted.

It can be seen that, apart from Finland and possibly Spain, there is a rather uniform prevalence of HD throughout Europe, with no clear distribution cline either from North to South or from East to West. Some of the early studies (e.g. Belgium) are likely to represent considerable under-ascertainment, but a prevalence of 4–7/100,000 is found over a large part of the continent. The data do not support the traditional view of an exclusively or even predominantly North European origin for the disorder.

The data for the United Kingdom offer an opportunity for a more detailed examination of the distribution and are shown in Fig. 2 and Table 3. No fewer than 15

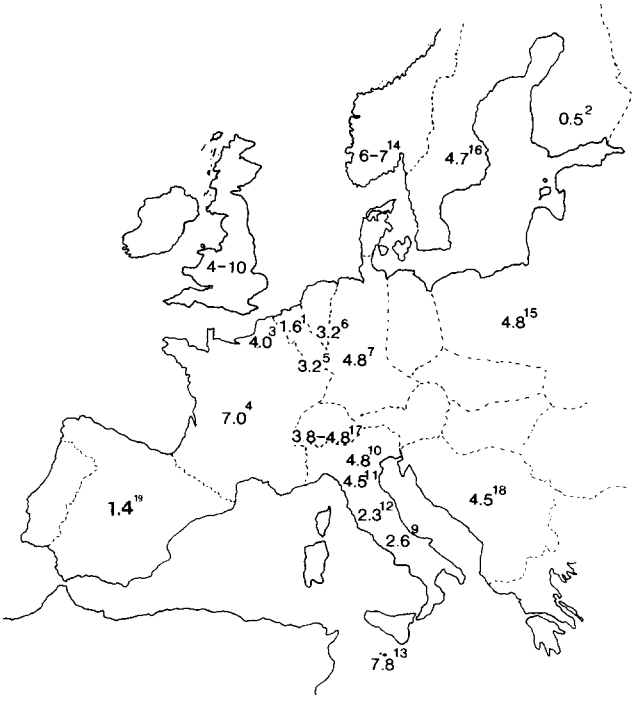

Fig. 1. HD in various European countries. (See Table 2 for details.) The *superscript numbers* refer to the published sources given in the table. It can be seen that there is a high prevalence rate for HD in most European countries where it has been intensively studied; Finland is an exception

Table 2. Prevalence estimates for HD in Europe (excluding UK)

Country	Map no.	Author	Prevalence per 100,000
Belgium	1	Husquinet (1970)	1.63
Finland	2	Palo et al. (1987)	0.5
France			
(Northern)	3	Petit (1970)	4.0
(Haute Vienne)	4	Leger et al. (1974)	4.8
Germany			
(Rhineland)	5	Panse (1942)	3.2
(Kassel)	6	Wendt and Drohm (1972)	3.2
(Federal Republic)	–	Wendt and Drohm (1972)	2.2
(Franconia)	7	Przuntek and Steigerwald (1987)	4.8
Iceland	8	Gudmundsson (1969)	2.7
Italy			
(Lazio)	9	Frontali et al. (1990)	2.56
(Emilia)	10	Mainini et al. (1982)	4.8
(Liguria)	11	Roccatagliata and Albano (1976)	4.5
(Toscana)	12	Arena et al. (1979)	2.34
(Florence)		Groppi et al. (1986)	4.1
Malta	13	Cassar (1967)	7.8
Norway	14	Saugstad and Odegard (1986)	6.7
Poland	15	Cendrowski (1964)	4.8
Spain	19	Ordonez (1970)	1.4
Sweden	16	Mattsson (1974)	4.7
Switzerland	17	Zölliker (1949)	3.8–4.8
Yugoslavia			
(Rijeka district)	18	Sepcic et al. (1989)	4.46

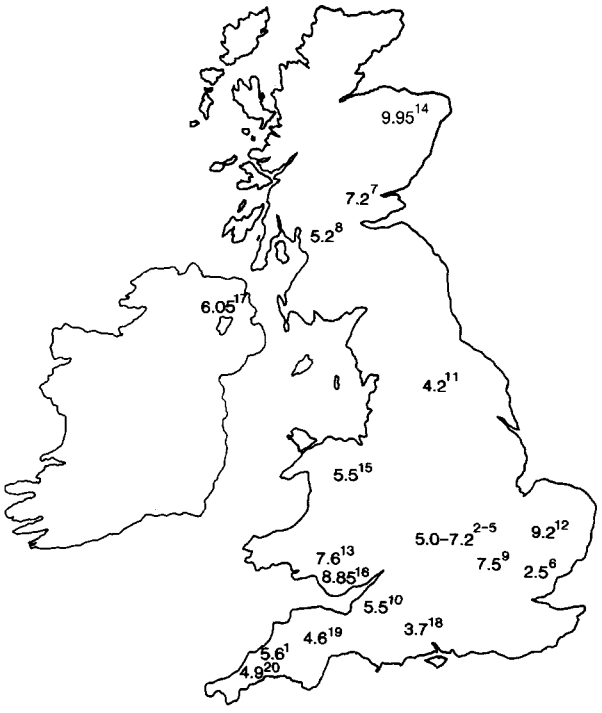

Fig. 2. HD in the United Kingdom.The map shows the results of prevalence studies based on defined geographical regions. (See Table 3 for details.) The *superscript numbers* refer to the published sources given in the Table

prevalence studies in different regions have been reported, while genetic registers based in regional clinical genetics centres form an increasingly important source of family data. Again these data provide no evidence for any single focus for the origin of the disorder in the UK, the highest prevalence estimates being for North East Scotland, East Anglia and Wales, all in widely separated parts of the country. There is no obvious correlation with regions of particular ethnic origin, whether Celtic or other, in contrast to the pattern seen for some other Mendelian disorders such as phenylketonuria (Harper 1976).

Among the estimates for well studied continental European countries that for Finland (0.5 per 100,000) is of particular interest, being an order of magnitude less than that of most other countries. Finland is well recognised as being genetically distinct from other populations and having a specific group of autosomal recessive disorders that reflect major differences in underlying gene frequency. Molecular study of Finnish HD families (Ikonen et al. 1990) has suggested more than one DNA marker haplotype associated with the disorder, so it could be argued that if one or a few common mutations are responsible for the high frequency of HD over most of Europe, the Finnish population must have diverged from the common stock before such mutations occurred or became widespread.

New populations of European origin

HD was originally described in North America in families of British descent; it is found in all major regions of the world whose population is predominantly of European origin, including North and South America and Australia as shown in Figs. 3 and 4 and the corresponding Tables 4 and 5. The surveys from North America are surprisingly few in number despite containing some of the most detailed studies; the United States death certificate data, discussed later, support a uniform distribution of the disease in different states, at least for the white population. The same can be said for Australia and New Zealand, with the exception of the island of Tasmania, where the high prevalence results from a single large kindred of English origin; recent re-assessment of the Tasmanian prevalence (Pridmore 1990b) has shown that it is less unusually high than suggested by the original studies (Brothers 1949), but that the one kindred still accounts for a high proportion of all cases.

South America is characterized by the largest and best studied focus of HD, that around Lake Maracaibo, Venezuela. The value of such isolates in studying HD is discussed later, but it should be pointed out that reports of HD have been widespread for most South American countries, including cases from Cuba (Arostegui 1890)

Table 3. Prevalence estimates for HD in the United Kingdom

	Publication year	Prevalence year	Region	Map no.	No. affected	Population	Prevalence $\times 10^{-5}$
Bickford and Ellison	1953	1950	Cornwall	1	19	340,941	5.57
Pleydell	1954	1954	Northamptonshire	2–5	13	263,000	5.0
Pleydell	1955	1954	Northamptonshire		17	263,000	6.5
Reid	1960	1954	Northamptonshire		19	263,000	7.2
Oliver	1970	1969	Northamptonshire		27	428,000	6.3
Heathfield	1967	1965	Essex	6	81	3,271,000	2.5
Cameron and Venters	1967		S.E. Scotland	7	84	1,163,877	7.2
Bolt	1970	1968	W. Scotland	8	154	2,959,600	5.2
Heathfield and MacKenzie	1971		Bedfordshire	9	30	427,970	7.5
Glendinning	1975	1965	Somerset	10	33	632,000	5.5
Stevens	1976	1966	Leeds and Yorkshire	11	133	3,190,000	4.17
Caro	1977	1971	East Anglia	12	54	584,415	9.24
Simpson and Johnston	1989	1984	Grampian, Scotland	14	47	462,891	9.95
Quarrell et al.	1988	1981	N. Wales	15	34	621,000	5.5
Quarrell et al.	1988	1981	S. Wales	16	153	1,728,000	8.85
Nevin N. and Morrison P.	1990[a]	1975	N. Ireland	17	93	1,536,000	6.05
Dennis N.	1990[a]	1987	Wessex	18	92	2,457,473	3.74
Garrett C.	1990[a]	1987	Devon	19	46	1,010,000	4.6
Garrett C.	1990[a]	1987	Cornwall	20	22	453,100	4.9

[a] Personal communication based on genetic registers: under-ascertainment of varying degree likely. The author is grateful for permission to quote these unpublished data

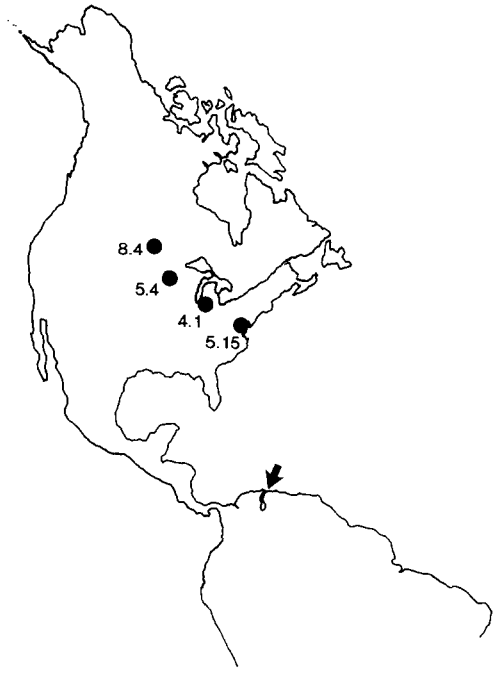

Fig. 3. North American prevalence estimates for HD. (See Table 4 for details.) The number of detailed population studies has been few in comparison with Europe. The Venezuela focus of HD is *arrowed*

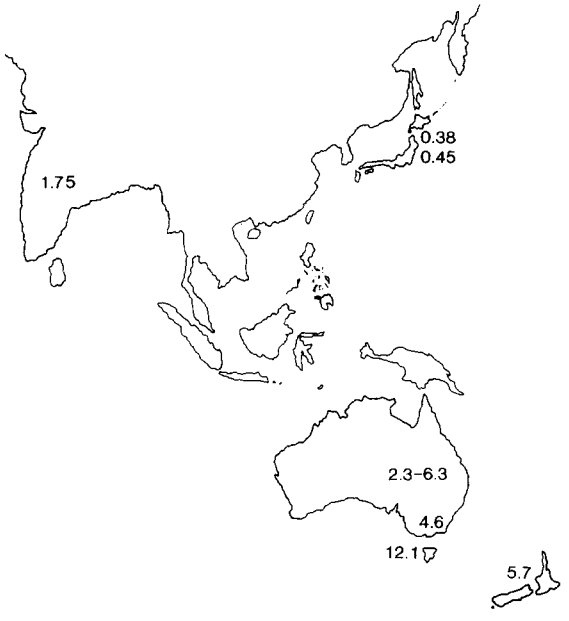

Fig. 4. HD in Asia and Australasia. (See Table 5 for details.) Note the exceptionally low prevalence for Japan. The estimate for India is based on a study of immigrants in the UK

and Brazil (Couto 1891) reported before the end of the last century.

There is no documented case of HD arising in the native populations of North or South America, nor in Australia, where its occurrence in Aboriginals has been shown to have a European origin (Gale and Bennett 1969). However, HD has been found to occur in New Guinea and some of the small island groups of the Pacific and would appear to antedate any European settlement there (Hetherington and Wechsler 1942; Scrimgeour

Table 4. Prevalence studies of HD: North America

Study	Publication year	Prevalence year	Region	No. affected	Population	Prevalence (per 100,000)
Reed et al.	1958	1940	Michigan	203	4,932,562	4.1 Overall 4.2 Whites 1.5 Blacks
Shokeir	1975		Manitoba/Saskatchewan	162	1,926,942	8.4
Pearson et al.	1955	1955	Minnesota	117	3,174,000	5.43
Folstein et al.	1987	1980	Maryland	217	4,217,000	5.15 Overall 4.94 Whites 6.37 Blacks

Table 5. HD in Australasia and Asia

Country	Study	Prevalence per 100,000
Tasmania	Brothers (1949); Conneally (1984)	17.4
Tasmania	Pridmore (1990b)	12.1
Victoria	Brothers (1964)	(4.58)
Queensland	Parker (1958)	2.3
Queensland	Wallace and Parker (1973)	6.3
New Zealand	Lintott C. (1990), personal communication	5.7
Japan	Kishimoto et al. (1957)	0.38
	Narabayashi (1973)	0.45
	Kanazawa (1983)	0.11
Indian subcontinent (UK immigrants)	Shiwach and Lindenbaum (1990)	1.75

1980, 1982). The interesting and plausible suggestion has been made that the gene could have been introduced by the crews of visiting whaling ships from North America, which were active in the sperm-whale fishery in the first half of the nineteenth century.

Scrimgeour (1983) searched the records of whaling voyages and found that a number of crew members had surnames present in known HD families from New England, recorded in the Davenport und Muncey archives, preserved at the University of Minnesota. While no direct link has been proven, the predominance of New Englanders in the whaling industry and the frequent sexual relations with islanders make this a reasonable hypothesis for these small populations, where genetic drift could have subsequently increased the gene frequency in some cases.

The origin of HD in populations derived from large scale immigration can be approached by examining the ethnic origins of HD patients in these countries. Data are available from several of the American studies and for Australia. The early study of Reed et al. (1958) found that 73 of 124 kindreds could not be traced back to an origin outside the United States, those that could being almost equally divided between Britain, Germany and other European countries for their origin. A corresponding study in Clinois (Falstein and Stone 1939) found a more frequent German origin, accounting for 27 of 62 kindreds, while Britain and Ireland had contributed only 9. Australian studies have likewise found a widespread origin of HD families (Wallace and Parker 1973), with South European countries also prominently represented. These results do not support the traditional concept of origin from a very small number of immigrant ancestors, either from Britain or elsewhere in Northern Europe. The pattern of HD closely reflects the composition of the population as a whole in its origin, with multiple introductions likely in all but the smallest or most isolated groups. The eugenic view advocated by Davenport and others (Davenport and Muncey 1916) that HD could have been kept out of America by imposing legislative restriction on the entry of a small number of individuals can be seen to be fallacious, though in any rapidly expanding population the possibility for spread of a late onset dominantly inherited disorder with minimal effect on genetic fitness is considerable.

Japan and other Asiatic countries

The remarkably low prevalence of HD in Japan is of great interest in relation to the possible origin of the disorder from a small number of mutations. Whereas for many parts of the world this could be attributed to lack of ascertainment, this is certainly not so for Japan, where well-developed neurological services and extensive neurological and neuropathological research would undoubtedly have identified most cases. Narabayashi (1973) reviewed the considerable number of publications on HD (over 40) from Japan; it is also of interest that some allied movement disorders such as chorea-acanthocytosis appear to be unusually frequent.

Kishimoto et al. (1957) undertook a prevalence study of HD in Aichi prefecture and obtained a prevalence of 0.38 per 100,000; an updated estimate of 0.45 per 100,000 was given by Narabayashi (1973). These values are one-tenth the prevalence of most European origin populations. A more recent estimate has been made by Kanazawa (1983) in Ibaraki prefecture, which gives an even lower prevalence (0,11 per 100,000). Only 3 living cases (1 doubtful) could be identified in a population of 2,638,280. Kanazawa points out that Kishimoto's original study was done in the part of Japan known to contain HD families, so it seems likely that HD is indeed exceptionally rare, though widely scattered.

There is no evidence for foreign admixture in the Japanese cases, but the reason for the lack of spread of the mutation or mutations raises points of great interest which will be resolvable only when the gene can be studied directly.

One possibility might be a higher degree of selection against the gene associated with the importance of genealogical information in Japanese society: it is perhaps relevant that the genetic study of Kishimoto et al. showed a more reduced genetic fitness (see below) than have other such studies. Alternatively, it could be postulated that a common Indo-European mutation had occurred and spread after the divergence of the ancestral Japanese population.

Detailed prevalence data on other Asiatic populations are few at present. The disorder is well recognised in Chinese populations from case reports, but has not been studied there systematically. Reports from the Indian Punjab (Chhutani 1957; Singh et al. 1959), Soviet Central Asia (Azerbaijan) (Kozlowa et al. 1986) and Turkey (Bayulkem and Turek 1961) all suggest that the disorder is not infrequent, while a recent study of UK immigrants from the Indian subcontinent (Shiwach and Lindenbaum 1990) has found an age adjusted prevalence of 1.75 per 100,000. These fragmentary data would be compatible with a true frequency approaching that seen in Europe.

African and American black populations

The work of Hayden (1979, 1981; Hayden et al. 1980a, b) in South Africa represents the only systematic study of HD in the continent. Hayden was able to document a substantial frequency of the disorder in the white population (of both Dutch and British descent), and he found a comparable frequency in the coloured (mixed race) population. Very few cases could be found in the much larger African origin population, suggesting a prevalence around ten times less. However, African cases have been documented in South Africa subsequently (Jouberg and Botha 1988), while isolated case reports have come from a variety of other African countries (Hutton 1956; Harries 1973; Osuntoken 1973; Haddock 1973), so that HD is certainly not unknown, even though likely to be less common than in European populations.

Studies of the United States black population originally suggested that HD was also rare in this group (Reed et al. 1958; Wright et al. 1981), but this view has had to be revised following the Maryland study of Folstein et al. (1987), which emphasised the difficulties of full ascertainment in this group and suggested that the apparent deficit in previous studies might not reflect a true lower prevalence. No European origin of the gene could be shown in most families.

Thus, the evidence on HD in people of African origin is currently inconclusive and would be compatible with the disorder occurring, probably at relatively low frequency, in indigenous African populations, most likely as a result of separate mutations, while in the American black population it is by no means certain that this disorder is exclusively of European origin.

Evidence from genetic studies

In addition to the geographical surveys already discussed, HD has been the subject of numerous quantitative genetic analyses; these are well discussed by Conneally (1984), while more recent genetic data have been reviewed by the author (Harper 1991). Only those aspects directly relevant to the epidemiology are mentioned here.

Table 6. Fertility and genetic fitness in HD

Study	Fertility			Fitness		
	Overall	Male	Female	Overall	Male	Female
Studies showing decrease						
Kishimoto et al. (1957)	–	–	–	0.65	0.61	0.68
Reed and Neel (1959)	0.82	0.66	0.98	1.03	0.82	1.25
Stine and Smith (1990)			Coefficient of selection 0.36			
Studies showing increase						
Marx (1973)	1.16	0.95	1.40	–	0.99	1.39
Shokeir (1975)	1.14	–	–	1.38	–	–
Stevens (1976)	1.36	1.09	1.61	1.39	1.03	1.52
Walker et al. (1983)[a]	1.25–1.34	1.43–1.55	1.0–1.30	1.46	1.66	1.29
Studies showing close to normal level						
Wendt and Drohm (1972)	0.95	0.93	0.96	0.96	0.93	1.03
Wallace and Parker (1973)	1.0	0.88	1.13	1.28	1.11	1.52
Mattsson (1974)	–	–	–	0.97	0.87	1.07
Mastromauro et al. (1989)	–	1.05	1.07	–	1.01	0.98

[a] General population estimates divided by decades of birth

Fertility

This has considerable implications for patterns of spread of the HD gene and for the extent to which recurrent mutation is necessary to maintain the prevalence at its relatively high level. The numerous studies of fertility and genetic fitness that have been carried out in HD have varied considerably (Table 6), both in absolute terms and in relation to unaffected sibs; HD is one of the very few disorders where an increased fertility has been suggested. Taken as a whole, however, it seems likely that fertility has been essentially close to normal. Though at different times and in different populations a slight increase or decrease may have occurred, it seems improbable that this has been large or consistent enough to influence the spread of the HD gene relative to its normal counterpart.

This conclusion would fit well with what we know in general terms of the disorder: that the great majority of HD patients have completed their families before developing symptoms. It would also suggest that the HD gene is likely neither to die out spontaneously, nor to replace the normal gene to any significant extent. Geographical variation of HD in individual populations should thus reflect the genetic history of that population in terms of origin, expansion and racial admixture, with the expected distortions from founder effect and rapid expansion in small isolated populations. The examples of Venezuela and Tasmania, among others, fit well with this view.

In future years, it is possible that strong selective pressures against the HD gene may result from the effects of genetic counselling and of prenatal and presymptomatic testing. It is unlikely that these have so far had any significant effect on the frequencies discussed here.

Mutation

All studies on mutation in HD agree that it is rare, and that new mutations account for only a very small proportion of all cases. Precise estimates are extremely difficult to make, since determining whether a particular case is indeed a new mutation is close to impossible for such a late onset disorder. Molecular evidence is now helping to document such cases, but it will remain uncertain how many of the supposed isolated cases of HD are indeed new mutations until we have specific tests for mutations in the gene. Table 7 summarises some of the estimates for mutation rate; it is clear that such low values would be unable to maintain the gene at its present high frequency over much of Europe if there were even a moderate selective disadvantage for it.

Table 7. Direct and indirect estimates of mutation rate in HD

Author	Direct	Indirect
Kishimoto et al. (1957)	–	0.67×10^{-6}
Reed and Neel (1959)	5.4×10^{-6}	9.6×10^{-6}
Wendt and Drohm (1972)	0	1.5×10^{-6}
Mattsson (1974)	5.0×10^{-6}	0.8×10^{-6}
Stevens (1976)[a]	$0.42–4.0 \times 10^{-6}$	0.07×10^{-6}
Hayden (1979)	0.13×10^{-6}	–
Walker et al. (1983)[a]	$0–1.0 \times 10^{-6}$	–

[a] Higher estimate includes all possible mutations

Heterogeneity

There is no evidence for more than a single genetic locus for HD, all of a large series of kindreds studied from many parts of the world showing linkage to markers on chromosome 4p (Conneally et al. 1989). There is evidence that some, but not all, of the differences in mean age at onset and death between families could result from separate mutations with differing phenotypic effect (Went et al. 1983), but these differences are outweighed by the very large within family variation.

Parental transmission affects and genetic imprinting

The one form of HD in which reproduction is greatly reduced is the juvenile form, accounting for 5%–10% of cases and showing marked clinical differences from the classical later onset disease (Bruyn 1968). Such cases are predominantly paternally transmitted (Merrit et al. 1969), a phenomenon that has given rise to much debate as to their basis. While there is currently no direct evidence for genetic imprinting in the region of the HD locus, the clear demonstration of "anticipation" in paternally transmitted HD (Ridley et al. 1991) suggests that a mechanism of this type could be responsible (Clarke 1990). An important alternative possibility is an unstable DNA repeat sequence, which has recently been shown to cause the anticipation seen in myotonic dystrophy (Harley et al. 1992; Harper et al. 1992).

Linkage disequilibrium

Although the HD gene itself has yet to be isolated, molecular analysis of distal 4p has shown a region in which DNA probes show linkage disequilibrium with the disorder (Snell et al. 1989; Theilmann et al. 1989). This has not only helped to define the location of the gene more precisely, but gives an indication that only a small number of common mutations are likely to be responsible. Since the disequilibrium has now been demonstrated in a number of separate European countries (Sandkuijl et al. in preparation), this supports the view already stated that any such mutation is likely to be of very ancient origin.

Data from "classical" epidemiological studies

In this review the evidence from family studies has been discussed first, since it has contributed by far the greater part of our knowledge on the distribution of HD. However, some data obtained by more traditional epidemiological methods do exist for HD (Kurtzke 1979; Schoenberg 1979). The personal view of the author is that the approaches that have proved valuable for such relatively common and non-Mendelian neurological disorders as

multiple sclerosis and motorneurone disease are less suitable for Mendelian disorders such as HD. In particular, reliance on HD death certificates is questionable, while the large number of secondary or undiagnosed cases encountered in thorough family studies is likely to make any study confined to primary cases a serious underestimate.

As already indicated, these data are subject to a number of disadvantages, notably that HD may not appear on the death certificate, either because the immediate cause of death was something else, or because the physician filling in the certificate may have wished to protect the family from adverse effects of HD being officially recognised as the cause. A further difficulty is that HD did not have a specific international code until 1968 (ICD 331.0, hereditary chorea). For the subsequent 10 years this category reflects HD accurately, since other causes of hereditary chorea are very rare, but unfortunately a further change in 1979 relegated HD to a subset (333.4) so that the three-figure code (often the only one completed) again contains other major diseases besides HD. Despite these problems, however, information on death rates is available from all areas without the need for special surveys or systems of collection. It is also likely to be comparable between regions in a way that individual surveys may not be. For this reason, the study of Hogg et al. (1979) of death rate data for the United States is important. Based on the data of 1968–1974, the study showed a remarkably uniform pattern of mortality from HD, with an age-adjusted death rate ranging only between 0.96 and 1.35 per million. A more detailed study including HD as a subsidary cause of death has given higher values (Lanska et al. 1988) but the main value of the data of Hogg et al. (1979) is the comparative picture that they give, not the absolute levels. Some data on HD mortality rates are also available; Table 8 summarizes some of these.

Death certificates can also be used longitudinally to follow any possible increase or decrease in HD. Caro (1977) noted a marked increase between 1959 and 1974, and that some increase was still present when the data were corrected for inaccuracy of certification, something that he had found to improve over this period. The same trend was noted and discussed by the Office of Health Economics (1980) report on HD. Figure 5 shows these data extended up to the present time; it can be seen that the increase has continued, though whether the accuracy of certification has also changed in the recent period is unknown.

The mortality rate is still considerably less than to be expected from the prevalence data shown in the detailed surveys. Broadly these data agree with the trend in different prevalence surveys carried out at different times in showing that both prevalence and mortality from recognized HD have increased. However, it would seem unwise to assume that any true increase in mortality can be inferred from these figures.

It is worth noting here that mortality data are of little use in monitoring changes resulting from genetic counselling and preventive programmes, since death rates reflect births occurring on average 50 years earlier. Hence the importance of birth-rate data based on those births known to be at risk, which will give a more sensitive indication of any recent changes (Harper et al. 1979). Any change in death rate is likely to result from factors operating half a century ago and these may be very different from those that are operating at present.

Table 8. Approximate average annual HD death rates per million population by sex and country. Data from Kurtzke (1979)

Country	Period	Male	Female
US total	1968–1974	1.1 (1.0–1.1)[a]	1.2 (1.1–1.3)
US white	1968–1974	1.2 (1.1–1.2)	1.3 (1.2–1.4)
US nonwhite	1968–1974	0.4 (0.3–0.6)	0.4 (0.3–0.5)
Sweden	1969–1974	1.7 (1.2–2.3)	1.7 (1.2–2.3)
Denmark	1951–1968	1.4 (1.1–1.9)	1.4 (1.1–1.9)
Denmark	1969–1975	1.8 (1.2–2.6)	1.9 (1.3–2.7)
England-Wales[b]	1960–1973	1.5 (1.4–1.6)	1.6 (1.5–1.7)
Japan	1969–1975	0.1 (0.1–0.1)	0.2 (0.1–0.2)

[a] Figures in parentheses are 95% confience intervals
[b] Code 331 total

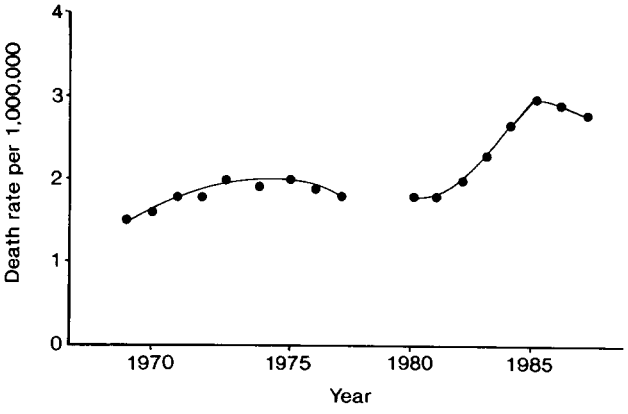

Fig. 5. Death rate from HD in England and Wales, 1968–1988. Three year moving averages, kindly provided by Office of Population Census and Surveys. Note that the discontinuity produced by the changes in ICD coding in 1978 does not appear to have altered the rate

Comparative surveys of neurological disorders

Surprisingly few detailed studies of the frequency of major neurological diseases in a population have been undertaken; this deficiency applies especially to inherited neurological disorders, whose low frequency by comparison with such disorders as stroke or senile dementia means that they have received little prominence in these studies, requiring a larger population base to give a meaningful prevalence. Thus the study of Kurland (1958) in Rochester, Minnesota, gave a prevalence of HD based on only two cases (admittedly his figure of 6.7 per 100,000 is close to that obtained from family studies).

A survey of major neurogenetic disorders in South Wales has recently been completed (MacMillan and Harper 1991), taking a population of just under one million

Table 9. Prevalence of inherited neurological disorders in South Wales[a]

Disorder	No. of living affected	Prevalence (per 100,000)
Huntington's disease	79	8.4
Neurofibromatosis (type 1)	125	13.3
Tuberous sclerosis	13	1.4
Hereditary spastic paraplegia	30	3.2
Charcot-Marie-Tooth disease	116	12.3
Myotonic dystrophy	65	6.9
Duchenne muscular dystrophy	40	8.8[b]
Becker muscular dystrophy	23	2.4[b]
Facioscapulohumeral muscular dystrophy	27	2.9

[a] Based on 1988 (June) total population, for Mid and South Glamorgan, of 939,300. Data from MacMillan and Harper (1991)
[b] Prevalence for males only

as the basis. While the data for HD were largely based on the authors' previous studies in the area, the comparative figures for other disorders (Table 9) confirm HD as one of the major diseases in this group. When the serious and progressive nature of its clinical effects are also taken into consideration, together with the large number of relatives potentially at risk, it can be appreciated that the overall "burden" of the condition for both families and the population as a whole is considerable.

HD in small populations

The importance of choosing a large and representative population for population and prevalence studies of HD has been emphasised, but the author would like to stress the value of also making careful studies of HD (and other genetic disorders) in small or isolated populations where the gene has achieved an unusually high frequency and where the disorder is thus correspondingly common. Not only does HD represent a major medical burden for patients, families and society in such populations, which may already be socially and economically deprived as the result of isolation, but they offer special, though different, opportunities for scientific study. It may be possible to trace precisely the spread of the HD gene in such a population in a way that is rarely possible in larger populations; the same HD mutation can be presumed to be present in all affected individuals, thus giving particular scope for the analysis of modifying factors; while if geneticists can enlist the cooperation of their social scientist colleagues, it may be possible to learn much about how the disorder interacts with society, something that may be of direct relevance to preventive strategies. Unfortunately it has rarely been possible to bring together these various elements in the case of HD. The best documented study of this nature that the author is aware of is the analysis of myotonic dystrophy in Northern Quebec (Saguenay), where the combined genetic, clinical and sociological approach has given a unique picture of the evolution of the disorder in a population and its overall effects on the community.

The focus of HD around Lake Maracaibo, Venezuela, numbering over 100 living affected individuals, all descended from a single ancestor, probably of European origin, is the largest and best studied HD isolate. It has been of special value in contributing to the localisation of the HD gene (Gusella et al. 1983), in the study of HD homozygotes (Wexler et al.1987) (who appear to be clinically identical to heterozygotes) and in longitudinal studies of the natural history of the disease (Penney et al. 1990). The smaller Tasmanian focus, recently restudied by Pridmore (1990a), is descended from a single ancester from Somerset, England. This population shows the latest mean age at onset (48.3 years) of any HD group and it is of interest that comparably late onset and benign kindreds have been recorded from the very same area of origin in England (Glendinning 1975), though no connection has yet been proved. Should they indeed prove to result from the same mutation it will be an important demonstration of how the HD phenotype resulting from a specific mutation can be retained over time in two widely differing geographical environments.

Other foci of HD include an isolated area of Northern Sweden (Sjögren 1936), the Moray Firth area of North East Scotland (Lyon 1962) and the Eastern Gwent Valleys of South Wales (Harper 1976). As already noted, none has received the detailed analysis of social structures that they deserve, and that will be of particular importance if effective preventive measures are to be achieved.

A final reason for the detailed documentation of individual HD populations is that once a specific mutation can be identified, a simple presymptomatic and prenatal test will be available for all members of the population sharing a common origin. (Whether such tests will be acceptable is an entirely different matter.) A comparable situation has already been encountered for beta-thalassaemia in such isolated populations as Sardinia, where a single mutation has likewise been shown to account for the great majority of cases. Thus in the near future a knowledge of the number and nature of the HD mutations in a specific population may well be an essential part of any genetic testing programme for the disorder. It could also be argued that a world wide database of HD mutations will be of value both for studies of phenotype in relation to type of mutation and for allowing the rapid choice of an appropriate specific test when prediction is requested. Such a resource would not require data on at risk individuals and hence would avoid many of the ethical constraints and problems posed by genetic registers.

General discussion

It can be seen from the work described here that the abundant data collected on HD from many parts of the world can be used to give a valuable, though incomplete and provisional, picture of its distribution and origins. Our knowledge of the basic genetics of HD, particularly of such factors as genetic fitness and mutation rate, can

also be used to assess the factors underlying the spread and distribution of the HD gene.

These traditional approaches have probably now reached the limits of their application for HD, but fortunately it seems likely that the unanswered questions will shortly be able to be approached directly as the result of isolation of the gene itself. Current molecular research (Shaw and Youngman 1991; Pritchard et al. 1991) has set narrow limits on the region in which it lies, a zone of linkage disequilibrium has been defined, while specific sequences in the relevant region are now being isolated and tested to determine which represents the gene. In the near future, it should be possible to detect specific HD mutations, to assess the frequency and distribution of the common ones, and to gain an idea as to how many there are altogether, as well as to correlate them with the observed phenotype.

It is certain that all of the work described in this review will require reassessment when this point is reached; it is likely that many of the conclusions will require revision. It is however, worth speculating as to what the specific molecular studies might find, and the author's own views on the likely outcome of this are given below.

1. More than one mutation will be found to have occurred at the HD locus.

2. A very small number of mutations, possibly a single common one, will be found to account for the great majority of HD cases in populations of European origin.

3. Any predominant mutation will be likely to have an extremely ancient origin, possibly dating back millenia.

4. No single focus in Northern Europe will be found as the point of origin of such a principal mutation.

5. Single populations, especially those that are small or isolated, will often contain a single mutation, but in large populations the origins will be multiple.

6. Phenotype will correlate poorly with specific mutations.

7. Most isolated cases thought to be HD on clinical grounds will indeed prove to result from mutations at the HD locus.

How many of these speculations will prove to be correct is a matter for conjecture; the only prediction that the author is prepared to make with confidence is that it will be possible to disprove or confirm most of them within the next 5 years.

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