Genetic aspects of hereditary motor and sensory neuropathy (types I and II)

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SUMMARY The genetic features of a series of 227 patients with hereditary motor and sensory neuropathy (HMSN) have been analysed. The series comprised 119 index cases from 110 families in which 108 affected relatives were identified. The cases were classified as having type I or type II HMSN on the basis of nerve conduction studies. Inheritance in the type I cases was autosomal dominant in 139 (45 families) and autosomal recessive in eight (four families) with 26 single cases. For the type II cases, 35 (17 families) were autosomal dominant and three (two families) autosomal recessive with 16 single cases. A significant excess of males was present in the combined single and recessive type I cases and in the type I index cases. No X linked pedigrees were identified.

The correlation coefficients for motor nerve conduction velocity between the index cases and their relatives suggested further genetic heterogeneity in the type I cases. Parent-offspring and sib-sib correlation coefficients for age of onset in the dominantly inherited type I cases were less than 0.5. There was therefore no strong suggestion of genetic heterogeneity in terms of age of onset.

The severity of muscle weakness did not differ between the dominantly inherited type I and type II cases. In both types males had higher weakness scores than females, but there was no difference for either type in relation to the sex of the affected parent.

Segregation analysis suggested that approximately 70% of the single generation type I cases were of autosomal recessive inheritance, whereas only about 25% of the single generation type II cases were recessive. Biological fitness was reduced in type II HMSN, which would support a higher proportion of new dominant mutations among the single cases of this type than in type I. Despite the excess of males in the type I single case/recessive category, a contribution of cases with X linked recessive inheritance is improbable. Single cases of HMSN, especially the type II form in view of its later onset, are likely to be unrecognised clinically and will be classified as 'cryptogenic' neuropathy. As in many affected subjects the degree of disability is minimal, a careful scrutiny of the relatives is merited in such instances.

Peroneal muscular atrophy is one of the most common inherited neurological disorders. Its prevalence has been estimated as 36 per 100 000 in Western Norway and 4.7 per 100 000 in the region of Newcastle-upon-Tyne, England. The latter is almost certainly an underestimate. In view of this, it is surprising that the only extensive published genetic analyses of this disease available are those of Bell and Skre. The main reason for this is that since the original description of the disorder by Charcot and Marie and by Tooth, considerable confusion has existed as to the nature of the disease and its variants.

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It is only in recent years, with the advent of nerve conduction studies and the more frequent use of peripheral nerve biopsy, that classification of the disorders that give rise to the clinical syndrome of peroneal muscular atrophy has been possible.

Charcot and Marie and Tooth independently described a progressive neuropathic disorder characterised by distal muscle wasting and weakness in the limbs, more severely affecting the legs. Sensory changes were unobtrusive but foot deformity was often evident. A tendency for the disease to be familial was noted. Dejerine and Sottas described a similar disorder in 1893 in two sibs; this was more severe with onset in infancy in one case. The occurrence of nerve hypertrophy was stressed and its
presence became synonymous with Dejerine-Sottas disease. It is only relatively recently that it was realised that hypertrophic neuropathy is the non-specific consequence of a chronic demyelinating neuropathy, being encountered in a variety of genetic and acquired disorders.7 8

Roussy and Lévy9 added to the existing confusion by describing cases similar to Charcot-Marie-Tooth disease, but characterised by tremor, ataxia, tendon areflexia, and pes cavus. It was proposed that such cases constituted a separate entity, but this was challenged almost immediately by Symonds and Shaw.10 Since then numerous case reports have suggested that peroneal muscular atrophy, the Roussy-Lévy syndrome, and Friedreich's ataxia may occur in the same family.11 12

In the mid 1950s, Henriksen13 and Gilliatt and Thomas14 showed that some patients with peroneal muscular atrophy had severely reduced motor nerve conduction velocities and others did not. With few exceptions15–17 there is now good evidence to suggest that peroneal muscular atrophy is divisible into two major genetically distinct groups in terms of both motor and sensory nerve conduction velocity.18–22 These groups are now generally referred to as hereditary motor and sensory neuropathy (HMSN) types I and II.23 24

Type I HMSN is characterised by severely reduced nerve conduction velocity and is associated morphologically with axonal loss, extensive segmental demyelination, and often hypertrophic changes. Type II displays normal or modestly reduced nerve conduction velocity, associated morphologically with axonal degeneration without conspicuous segmental demyelination. Other genetic disorders that give rise to a similar clinical phenotype are distal spinal muscular atrophy25 26 and distal myopathy.27 They can be distinguished on neurophysiological and histological grounds.

It is now accepted that the Roussy-Lévy syndrome is an expression of the gene for type I HMSN. The reasons for this are twofold. The Roussy-Lévy syndrome occurs in patients with other family members showing the typical clinical features of type I HMSN.18–22 Furthermore, this syndrome is not sharply distinct clinically from HMSN type I as there is a continuous spectrum of clinical features within this disorder with tremor or ataxia or both being absent, mild, moderate, or marked, even within the same family. Secondly, the neurophysiological and histological features of the Roussy-Lévy syndrome and type I HMSN are identical. Lapresle and Salisachs28 demonstrated hypertrophic changes with the characteristic onion bulb formations in one of Roussy and Lévy's original patients.

As a result of these advances in the classification of peroneal muscular atrophy, a discussion of the genetics of these disorders is now required. Although autosomal dominant, autosomal recessive, X linked dominant, and X linked recessive forms of peroneal muscular atrophy have been described,1 2 29 30 documentation has often been less than ideal. Moreover, there are still problems which arise in counselling single cases.

A study on a large series of 261 patients with peroneal muscular atrophy has recently been undertaken. Of these, 34 were instances of distal spinal muscular atrophy and they have been described elsewhere.26 The remaining 227 were suffering from HMSN types I and II. Their clinical features have been documented separately.28 This paper reports the genetics of these disorders.

Methods and results

Clinical series

This study was undertaken on a consecutive unselected series of patients referred to one of us (PKT) at the Royal Free Hospital, the Royal National Orthopaedic Hospital, and the National Hospital for Nervous Diseases, London, between 1966 and 1978. Each index case was examined clinically and neurophysiological studies performed. Only cases which would be diagnosed as peroneal muscular atrophy alone have been included; those with more complex syndromes and additional features such as extensor plantar responses have been excluded.

The series comprised 119 index cases from 110 families. An index patient was defined as a subject with the disease, independently ascertained, who brought the family to the notice of the study. Of the families, 32 were unavailable for study or uncooperative, but reliable information was obtained about 26 of them. Two patients were adopted and no details were known about their relatives. Near relatives of the index cases were examined and neurophysiological studies performed when possible. A clinical examination was undertaken on 383 relatives and 108 were found to be affected. Of these, 60 had nerve conduction studies performed. No clinical abnormality was detected in 275 of the relatives and this was confirmed electrophysiologically in 40. No clinically normal subject had abnormal motor or sensory nerve conduction studies.

Classification

Patients were classified as having type I or type II HMSN on the basis of median motor nerve conduction velocity (MNCV) as described by Thomas
and Calne and Harding and Thomas. Index cases with a median MNCV of less than 38 ms\(^{-1}\) were designated as type I HMSN and those with velocities greater than this as type II. This method of classification gives near complete concordance for MNCV between families and there is no evidence that the type II group can be subdivided any further in terms of MNCV. There is an indication of heterogeneity for MNCV in the type I group in terms of the correlation coefficient for MNCV (r = 0.71, p < 0.05) between the index cases and relatives.22

In view of this, the type I group has been further analysed by calculating the correlation coefficient of age of onset between parents and offspring and pairs of sibs. This yields values for r of 0.36, p < 0.01 (parent-offspring sibs) and 0.48, p < 0.001 (sib-sib pairs).

Although the correlation coefficient for MNCV suggests that type I HMSN may be caused by more than one gene, there is no evidence that these genes give rise to disorders with different ages of onset. There is no obvious way of further subgrouping individual cases in terms of MNCV; the classification has therefore been confined to types I and II HMSN. These two categories have been further subdivided depending on whether inheritance was autosomal dominant or autosomal recessive. An additional sub-group consists of single cases. A summary of this classification is shown in table 1. It will be seen that the large majority of cases are dominantly inherited. The recessive families consist of six pairs of sibs. Their parents were examined clinically and electrophysiologically in nearly all instances. The clinical features of these cases have been described separately.

**SEX RATIOS**

The ratio of males to females in index cases and in all cases from each type and sub-group of HMSN is shown in table 2. The differences were tested using the null hypothesis that the observed proportions did not differ from the expected 50:50. Yates’s \(\chi^2\) test was used.22 The proportion of males to females in normal sibs and affected parents of dominant cases is also shown in table 2. It will be noted that there are two groups in which a significant excess of males occurs (both type I HMSN). This was so for the total number of index cases, as a result of the male excess in the single and recessive cases combined.

**SEVERITY**

Severity was assessed in terms of muscle weakness as this is the major cause of disability in HMSN. Weakness was graded from 0 to 2 in the upper and lower limbs and the scores combined. Each patient was therefore allocated a weakness score ranging from 0 to 4. In a separate communication22 it was shown that mean weakness scores for single generation cases of HMSN type I are higher than those for the dominantly inherited cases, in keeping with the generally held view that the recessive form of a disorder tends to be more severe than the dominant.

Recent reports have indicated that offspring of affected mothers are more severely affected than those of affected fathers in certain dominantly inherited neurological disorders, such as dystrophia myotonica and neurofibromatosis.34 In view of this, the mean weakness scores of offspring of affected mothers were compared with those of offspring of affected fathers. The scores are 1.78 ± 1.1 and 1.87 ± 1.2, respectively, for type I (p > 0.05), and 1.79 ± 1.3 and 1.70 ± 1 for type II (p > 0.05).

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**Table 2: Sex distribution**

<table>
<thead>
<tr>
<th>Type</th>
<th>No of cases</th>
<th>Male</th>
<th>Female</th>
<th>(\chi^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I total</td>
<td>90</td>
<td>83</td>
<td>0.21</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Index cases</td>
<td>54</td>
<td>29</td>
<td>6.94</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Index cases: dominant</td>
<td>31</td>
<td>18</td>
<td>2.94</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Dominant cases</td>
<td>68</td>
<td>71</td>
<td>0.11</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Recessive cases</td>
<td>6</td>
<td>3</td>
<td>0.5</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Single cases</td>
<td>18</td>
<td>8</td>
<td>3.11</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>Reccessive + single cases</td>
<td>23</td>
<td>11</td>
<td>4.65</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

| Type II total | 29 | 25 | 0.17 | >0.05 |
| Index cases | 21 | 15 | 0.69 | >0.05 |
| Index cases: dominant | 8 | 9 | 0.23 | >0.05 |
| Dominant cases | 15 | 20 | 1.03 | >0.05 |
| Recessive cases | 2 | 1 | 0 | — |
| Single cases | 12 | 4 | 3.06 | >0.05 |
| Affected parents of dominant cases | 10 | 19 | 3.44 | >0.05 |
| Normal sibs of dominant cases | 24 | 37 | 3.21 | >0.05 |
| Normal sibs of single + recessive cases | 27 | 22 | 0.32 | >0.05 |

**Table 1: Classification of HMSN**

<table>
<thead>
<tr>
<th>Type</th>
<th>No of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>173</td>
</tr>
<tr>
<td>Index cases</td>
<td>83</td>
</tr>
<tr>
<td>Secondary cases</td>
<td>90</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>139 (45 families)</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>8 (4 families)</td>
</tr>
<tr>
<td>Single cases</td>
<td>26</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
</tr>
<tr>
<td>Index cases</td>
<td>36</td>
</tr>
<tr>
<td>Secondary cases</td>
<td>18</td>
</tr>
<tr>
<td>Autosomal dominant</td>
<td>35 (17 families)</td>
</tr>
<tr>
<td>Autosomal recessive</td>
<td>3 (2 families)</td>
</tr>
<tr>
<td>Single cases</td>
<td>16</td>
</tr>
</tbody>
</table>
There is therefore nothing to suggest a similar maternal effect in HMSN.

**Segregation analysis**

**Autosomal dominant cases**

The proportion of affected to unaffected offspring and sibs for the index cases of the presumed autosomal dominant families is shown in table 3. These figures include subjects affected or unaffected by reliable history, as well as those seen personally. The null hypothesis that the expected proportions would not deviate from the expected 1:1 was tested by using the formula

\[ \chi^2 = \frac{(A-N)^2}{A+N} \]

for affected and \( N = \) total unaffected.\(^{35}\)

In both types of HMSN the ratio of affected to unaffected was significantly less than 1:1. Although this method of calculation is theoretically desirable as it removes ascertainment bias, the resulting ratio is likely to be less than 1:1 as the index cases are removed from the numbers of affected cases. Furthermore, index cases are likely to be in younger generations and therefore may not yet have reproduced or completed their families. Accordingly, the proportion of affected to unaffected offspring of all affected parents in the pedigrees were calculated using the same formula. These ratios are also shown in table 3. Generations were omitted if insufficient information was available.

The ratio of affected to unaffected does not differ significantly from 1:1 in type I HMSN. However, in type II the proportion differs highly significantly with a majority of unaffected subjects. Type I HMSN presents during the first decade in over 60% of cases; in type II HMSN only 25% develop symptoms before the age of 10, 35 to 40% in the second decade, and a significant number (35 to 40%) after the age of 20, some not until the 7th decade.\(^{22}\) In view of this it would seem reasonable to suggest that family members under the age of 20 at the time of the study may appear unaffected and yet later develop the disease. The ratio of unaffected to affected was therefore tested against an expected 1:1 after removing all cases aged under 20 years. This yielded a value for \( \chi^2 \) of 1.09 (\( p > 0.05 \)). When only subjects under the age of 10 were removed, \( \chi^2 \) was 3.64 (\( p > 0.05 \)).

**Autosomal recessive and single cases**

Six families (four type I and two type II) had pedigrees suggesting definite autosomal recessive inheritance. One family contained two affected male sibs and therefore theoretically could have been X linked recessive. The other families contained affected males and females. The parents were all normal and most of those who were still living were examined clinically (8/9) and electrophysiologically (6/9). In three families (one type I, two type II), the parents were first cousins. Of the single cases, three patients (type I) gave a history of affected sibs and normal parents. Two other single cases had consanguineous parents, one pair (English, type I) were second cousins and one (Iraqi, type II) first cousins. In view of the relatively high consanguinity rate in Iraq, the latter is not necessarily of significance.

As this series was collected by multiple incomplete ascertainment, Weinberg's proband method\(^{38}\) was used to analyse the autosomal recessive and single cases (where accurate information was available). This is a direct calculation of the proportion of affected sibs of index patients, and the method is self-correcting, whether ascertainment of index cases is single, multiple, or truncate.\(^{35}\) The standard error (SE) of segregation ratios was calculated using the formula

\[ SE = \sqrt{\frac{p(1-p)}{n}} \]

where \( p = \) segregation ratio and \( n = \) total number of sibs of index patients. This is admittedly oversimplified, as calculation of the standard error in the Weinberg proband method is complex.\(^{38}\) More complex methods of calculating standard error are available,\(^{38}\) but there is no universal agreement as to their assumptions or statistical validity.\(^{39}\) Confidence limits (CL) of 95% were obtained from: 95% CL = \( p \pm 1.96 \times SE \). It is unlikely that limitation of family size occurs in HMSN as the diagnosis is usually made after the family has been completed. The results of the segregation analyses are shown in table 4.

In type I HMSN the results from cases confined to single sibships suggest that between 28 and 100% of the affected cases are autosomal recessive. The value of \( p \) obtained (0.164 ± 0.096) is not significantly different from 0.25 and it is therefore compatible with recessive inheritance in all the single cases.

**Table 3** Ratios of affected : unaffected subjects in families with presumed dominant inheritance

<table>
<thead>
<tr>
<th>Type</th>
<th>No of affected</th>
<th>No of unaffected</th>
<th>( \chi^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I: offspring and sibs of index cases</td>
<td>38</td>
<td>64</td>
<td>7.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Type II: offspring and sibs of index cases</td>
<td>5</td>
<td>23</td>
<td>12.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type I: offspring of affected parent</td>
<td>181</td>
<td>160</td>
<td>1.17</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Type II: offspring of affected parent</td>
<td>36</td>
<td>61</td>
<td>6.97</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Type II: cases under 20 excluded</td>
<td>33</td>
<td>41</td>
<td>1.09</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Type II: cases under 10 excluded</td>
<td>36</td>
<td>53</td>
<td>3.64</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

A E Harding and P K Thomas
In type II HMSN, the results suggest that a smaller proportion of the single cases are recessively inherited (25%). Admittedly the number of type II families is small and several of the sibships are large.

**BIOLOGICAL FITNESS**

Biological fitness (BF) was calculated for the index cases of autosomal dominant types I and II HMSN. Only index cases aged over 40 were included and the numbers are accordingly small (17 type I and 10 type II). Family size was compared with that of the general population, rather than that of normal sibs; the latter would have involved very small numbers and it cannot be assumed that the presence of a genetically determined disorder in a family only limits the number of offspring of affected members. The mean family size of the general population was estimated at 2–15, on the grounds that family size has only varied between 2–0 and 2–3 since 1928 according to the Registrar General's statistics. The mean family size for type I HMSN was 2·23 ± 1·52 (t = 0·625, p > 0·5, BF 1·04). In type II HMSN the mean number of offspring per index case was 1·6 ± 0·97 (t = 5·9, p < 0·001, BF = 0·74).

**Discussion**

The division of HMSN into two groups (types I and II) based on nerve conduction velocity was first discussed by Dyck and Lambert\(^{18,19}\) and has been confirmed by other authors.\(^{17,20–22}\) Concordance within families suggests that this division has a genetic basis and that at least two different autosomal loci are involved in the genesis of the disorder. There are important clinical differences between the two groups.\(^{22}\) The current series, which is the largest reported to date, provides statistical evidence that there may be further genetic heterogeneity in terms of MNCV in type I HMSN (r = 0·71).

Haldane\(^{40}\) has argued that in a condition determined by more than one gene, each determining the age of onset, parent-offspring and sib-sib correlation coefficients will each approach unity. Harris and Smith\(^{41}\) have suggested on theoretical grounds that if such correlation coefficients are 0·5 or more, there is a suspicion that there are two or more genes mimicking one another. In the data (included in the present series) presented by Thomas et al,\(^{53}\) correlation coefficients for age of onset of symptoms in parent-offspring and sib-sib pairs were 0·35 and 0·5, respectively, in families with reduced (type I) velocities. Values calculated from the present series give correlation coefficients of 0·36 for parent-offspring pairs and 0·48 for sib-sib pairs. The former value is significantly less than 0·5 so it is unlikely, if more than one gene produces HMSN, that such genes give rise to disorders with different ages of onset.

It is notable that the parent-offspring correlation coefficient for age of onset is less than for sib pairs. The mean age of onset in parents was 20·9 ± 10·9 years and that of offspring 9·6 ± 6·2 years (t = 7·58, p < 0·001). Penrose\(^{42}\) reported similar but more marked differences in data on dystrophia myotonica, and discussed the problem of apparent 'anticipation'. There are several possible explanations for low parent-offspring and high sib-sib correlation which are more plausible than the theory of anticipation. Affected parents are more likely to be ascertained if their age of onset is relatively high as severely affected subjects with an early age of onset will tend not to reproduce. Conversely, offspring with an early age of onset will be selected more frequently; some offspring may develop the disease after the time of study. Another important source of variation between parents and children and similarity between sibs is the fact that parents and offspring very rarely possess identical alleles, whereas sibs have 50% in common. If an allelomorphic effect is important in HMSN, it could well explain the marked intrafamilial variation in severity, age of onset, and other features. This variation makes further division of the type I group on grounds other than statistical a matter of difficulty.

In the present series, the majority of families (91%) exhibit autosomal dominant inheritance. In these families there is no significant difference in the sex ratio of affected subjects, and in the type I group there is no significant departure from the expected 1:1 ratio of affected to unaffected progeny of affected parents. If all subjects are included in the data, the ratio departs from 1:1 in the type II group,
but not if allowances are made for the later age of onset in this disorder. Most of the families with HMSN in published reports show autosomal dominant inheritance. Woratz has produced evidence of X linked dominant inheritance in HMSN, reporting a large pedigree with affected males transmitting the disorder to all of their daughters but to none of their sons, and affected females to approximately half of their offspring of either sex. This is the only large family with possible X linked dominant inheritance published, and the pattern of transmission could result from chance. None of the large pedigrees in the present series suggests X linked dominant inheritance. Some of the smaller ones could, but the overall sex ratios of affected and unaffected sibs and affected parents do not depart from 1:1. If X linked dominant inheritance occurs in HMSN, it must therefore be a rare event.

None of the families described in this paper exhibits X linked recessive inheritance. With this in mind, it is of interest to note that there is an excess of males in the type I single cases, although this is not statistically significant. It would seem unreasonable to suggest that this is because of X linked inheritance in the absence of any definite pedigrees. One family in the type I group contained only two affected male sibs, but no other affected males; two maternal uncles were normal. The inheritance in this family was presumed to be autosomal recessive. X linked inheritance has been reported in HMSN particularly in older publications. Herringham reported a large kinship in which 20 affected males occurred in four generations. This kinship has frequently been cited as an example of X linked recessive HMSN, but on close examination of this pedigree it is seen that one instance of male to male transmission occurred. There are families described in which the pedigrees would comply with X linked recessive inheritance. However, very few of the 'carrier' females in these families were examined clinically and obviously nerve conduction studies were not performed. Church stated that some of these females had 'weak ankles' which would suggest that they were mildly affected. Skre described a family stated to exhibit X linked recessive inheritance. The parents of the affected boys were not examined but some of their female sibs and offspring were stated to have 'unspecific neuropathy'. This could well have been because of incomplete expression of a dominant gene. A recent paper reporting lack of a linkage with Xg blood groups in X borne Charcot-Marie-Tooth disease gives very little information about the family studied. It was stated to show 'X borne partially dominant inheritance'. It is highly likely that most of these families in which X linked recessive inheritance was claimed were dominantly inherited with incomplete expression in the females. The finding in the present series that males are more severely affected than females would support this postulate, as would the fact that more of the asymptomatic patients (67%) were female than male. Similarly there are more males than females among the index cases of dominant families (39 of 66), although this difference is not statistically significant. The total number of index cases shows a significant excess of males. There is therefore no convincing evidence that X linked recessive HMSN exists.

It is of interest to note, in relation to sex ratios, that early published reviews quoted affected male to female sex ratios of up to 5:1, whereas Becker in a more recent review of 586 dominant cases, found 327 males and 259 females. This is probably the result of more complete ascertainment of affected subjects in latter years. Some affected subjects in the present series had minimal physical signs, such as absent ankle jerks and mild weakness of dorsi-flexion and evasion at the ankles. These mildly affected subjects are more likely to be female. It is therefore important, particularly in counselling, to examine parents and sibs, and to perform nerve conduction studies if there is any doubt whatsoever whether they are affected. In the present series, no clinically normal subject had abnormal sensory or motor conduction.

This study has shown that both types of HMSN may display autosomal recessive inheritance. There are approximately 50 published reports of probable recessive HMSN. As very few of the parents were examined in these families, it is quite possible that some of the cases were autosomal dominant. Only about 10% of families with both types of HMSN overtly demonstrated autosomal recessive inheritance in the current series.

The proportion of single cases in this series was not high, although a considerable number of index cases gave a negative family history initially. Close questioning and examination of the relatives provided evidence for autosomal dominant inheritance in 17 families which were originally stated by the probands to be normal. In addition to these families, several patients gave a vague history of 'arthritis' in previous generations, which proved to represent subjects with undiagnosed HMSN.

In type I HMSN, segregation analysis suggests that between 28 and 100% of the single generation cases were recessively inherited. In type II, the proportion was considerably less, being in the region of 25% (0 to 52). In view of these figures, it is of interest to note that biological fitness is reduced in type II (0.74) HMSN but not type I (1.04). These results indicate that the proportion of new dominant
mutations per generation would be in the order of 25% of dominantly inherited cases of type II HMSN, whereas in type I HMSN the number of mutations would be small. The difference in biological fitness between the two disorders is very surprising considering the later age of onset of type II HMSN, but the mean family size of type II index cases is highly significantly less than that of the general population, even though the numbers here are small.

There are other possible explanations, apart from mutation, for the occurrence of the remaining single cases in type II and, if any, type I HMSN. In a few instances it is likely that identification of the father was incorrect and that they are in fact dominantly inherited. A proportion may be non-genetic phenotypic copies. This last possibility is probably particularly applicable to type II HMSN. Since this disorder has a later age of onset than type I HMSN, the incidence of foot deformity is lower and its distinction from other longstanding chronic axonal degenerations can be difficult. This type of neuropathy is frequent among ‘cryptogenic’ cases (P K Thomas, unpublished data). Thus, the diagnosis of HMSN, particularly type II, should be considered in cases of undiagnosed neuropathy, especially if the course is chronic and foot deformity is present. Dyck and Ovitt52 diagnosed HMSN in 23 of 47 such patients by clinical and neurophysiological examination of near relatives. These cases constituted 12% of a series of 190 patients with undiagnosed neuropathy.

It is possible to calculate empirical recurrence risks for prospective sibs of single cases from the segregation ratios presented here. For type I HMSN, the risk is approximately 1 in 6, but it is only 1 in 16 for type II HMSN. These figures illustrate to a certain extent the importance of distinguishing between the two disorders, although counselling parents of single cases of type II HMSN is not a frequent problem in view of the minority (25%) of cases presenting in the first decade. Counselling single cases who wish to have children is more difficult; the maximum risk to children of patients with type I HMSN would be 1 in 8 (assuming 30% are new dominant mutations, which is probably an overestimate). In type II HMSN the risk would be higher, in the region of 1 in 5, as there is good reason to suggest a higher proportion of dominant mutations in this disorder. These estimates are approximate and cautious; reliable figures can only be given when segregation analyses have been performed on the children of these single cases. In counselling asymptomatic sibs or children of affected subjects from dominantly inherited families who wish to know the risks of producing affected children, the available evidence indicates that in type I HMSN reduced nerve conduction velocity is present in infancy, whether or not the subjects are symptomatic.53 A clinically and electrophysiologically normal subject can therefore be given a zero risk. The situation is not as easy in type II HMSN in view of the frequently delayed onset of symptoms and the less obtrusive changes in nerve conduction. A normal clinical and electrophysiological examination in childhood or adolescence may not exclude the later development of the disorder. It should not be forgotten that the expression of both genes varies considerably even within families: a severely affected subject may have minimally disabled children and vice versa.

In view of the large volume of family data accumulated during this study, it was considered that an appendix of pedigrees and clinical information would be too cumbersome for the purposes of publication. Pedigrees and further details concerning some of the families described here are available elsewhere.22 23 31 Other information may be obtained from the authors on request.

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