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Linkage of autosomal dominant type I hereditary motor and sensory neuropathy to the Duffy locus on chromosome 1

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SUMMARY Data from English families confirms the probable linkage of the loci for autosomal dominant type I hereditary motor and sensory neuropathy (HMSN) and the Duffy blood group. The locus for autosomal dominant type I HMSN is in chromosome 1 near the centromere, about 15 centimorgans from the Duffy locus. The linkage between type I *HMSN* and the *Duffy* locus and the two recombinants found between *Duffy* and type II *HMSN* support the hypothesis that there are at least two genetic variants of autosomal dominant HMSN.

Cases diagnosed clinically as peroneal muscular atrophy or Charcot-Marie-Tooth disease[1,2] may be classified according to nerve conduction and nerve biopsy studies into hereditary distal spinal muscular atrophy and hereditary motor and sensory neuropathy (HMSN).[3–7] In cases of distal spinal muscular atrophy there is evidence of denervation in affected muscles, but motor conduction velocities (MCV) and sensory action potentials are within the normal range.[5] The pathological process is thought to affect anterior horn cells. In HMSN electrophysiological studies demonstrate abnormalities of both motor and sensory fibres. Dyck and Lambert,[8,9] in their original classification, had described two main types of Charcot-Marie-Tooth disease. The first consisted of patients with low MCV, and was termed the "hypertrophic" form as the nerves may be clinically enlarged and nerve biopsy showed onion bulb formation with an expanded transverse fascicular area and evidence of extensive segmental demyelination and remyelination. The second comprised patients with normal or slightly reduced MCV and was termed the "neuronal" form, the putative pathology being degeneration of anterior horn and dorsal root ganglion cells. Nerve biopsy showed no evidence of hypertrophy or segmental demyelination and remyelination, although later a minor degree had been found to occur.[6] These two forms, Charcot-Marie-Tooth 1 and 2 correspond to types I and II HMSN respectively. In both, autosomal dominant and recessive inheritance and single cases have been described.[3,4] Thomas and Calne[10] observed that in autosomal dominant HMSN, plotting MCV for propositi against that for affected relatives yielded a strongly positive correlation with clustering into two groups, one with substantially reduced velocity (type I) and another with normal or slightly reduced velocity (type II). This finding suggested that the distinction between the two types had indeed a genetic basis. More recently it has been proposed that there may be further genetic heterogeneity within autosomal dominant type I HMSN.[3]

The separation of dominantly inherited HMSN into two types has been criticized on the grounds that there is an overlap in MCV between the two types,[11] although such an overlap is not observed if sensory conduction velocity is used as the discriminator.[7] The same is true for the findings obtained on nerve biopsy.[7] The possible existence of two (or more) genetically distinct forms could be illuminated in a more direct way if it were possible to show that they are related to different genetic loci, either in the same or different chromosomes. We report here our findings in six English families with autosomal dominant HMSN studied for various

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genetic markers. A summary of the genetic data has already appeared elsewhere;[12] it supports linkage of HMSN type I with the Duffy blood group locus. Linkage between Charcot-Marie-Tooth disease and this locus has recently been suggested by Bird *et al*.[13 14]

Materials and Methods

Six families with autosomal dominant HMSN were studied. Five published previously by Thomas *et al*[15] were revisited and re-examined. A few additional members were examined both clinically and electrophysiologically. Four families (Nos 4, 8, 9, and 10)[15] are type I and one (No 14)[15] is type II. An unpublished family from Wessex with type II HMSN was also studied. In this, one member had had a sural nerve biopsy and median nerve MCV in affected members ranged from 33 to 52 m s^{-1}. Table 1 summarises the type and total number of families with tested and affected individuals.

Table 1 *Families studied with autosomal dominant HMSN*

	Families n	*Individuals*	
		Tested (n)	*Affected (n)*
Type I	4	37	22
Type II	2	38	13
Total	6	75	35

Blood and saliva were obtained and tested for the following genetic markers:

(a) Red cell antigens: ABO, MNSs, P, Rh, K, Kp, Lu, Fy, Jk.
(b) ABH secretor status.
(c) Red cell isozymes: ACP-1, ADA, PGM-1, ESD, AK-1, PGD, GLO, PGP.
(d) Serum groups: Gc, Hp, Gm, Km.
(e) HLA antigens: HLA-A, HLA-B, HLA-C.

PGP, Gm and Km were not tested in family 8 and the Wessex family. The latter was also not tested for GLO and HLA. Seventeen of the 25 markers studied have been definitely or provisionally assigned to specific chromosomes (see table 2). Linkage analysis was performed using the lod score method,[16] which enables all available information from families of different sizes and mating types to be pooled and used. The lod score represents the total relative probability of linkage versus independent inheritance and is expressed as a logarithm of the odds favouring linkage. Linkage is considered established if the lod score at any recombination fraction is three or more.

Table 2 *Known assignments of markers tested*

Chromosome	*Markers*
1	Rh Fy PGM-1 PGD
2	ACP-1 (Jk) (Km)
4	MNSs Gc
6	HLA GLO
9	ABO AK
13	ESD
14	Gm
16	Hp
20	ADA

The Duffy blood group system

The positive findings of our study relate only to this genetic marker. The Duffy blood group was initially recognised by Cutbush *et al*[17] in a haemophiliac who developed a haemolytic transfusion reaction and was found to have a new isoantibody detectable by the indirect Coombs test. It was termed anti-$Duffy^a$ and the antigen in the donor's red cells reacting with it, $Duffy^a$ or Fy^a.[17 18] Soon after, a second allele $Duffy^b$ or Fy^b was found.[19] Sanger *et al*[20] observed that most negroes did not have either Fy^a or Fy^b and named this new silent gene *Fy*. A rare gene Fy^x which makes a small amount of Fy^b antigen and several new Duffy antibodies have been described but are of no relevance to our study.[21] The gene frequencies in Caucasians are Fy^a 0·425, Fy^b 0·557, Fy^x 0·016, *Fy* 0·002.[21] The locus for congenital zonular cataract has been found to be linked to the *Duffy* locus.[22] In 1968, Duffy had the distinction of being the first locus in man to be assigned to a particular autosome when it was demonstrated that an inherited visible abnormality of chromosome 1 called uncoiler was linked to the *Duffy* locus.[23]

Nomenclature The Duffy phenotype refers to the reactivity of red blood cells of an individual with anti-Fy^a and/or anti-Fy^b sera. If they react the + sign is used, if they do not the − sign is used. The genotype refers to the gene controlling the presence of the antigen in those red cells. The genes Fy^a and Fy^b are codominant alleles. Accordingly, an individual whose red cell group is Fy (a+ b+) will have the gene Fy^a in one chromosome and the gene Fy^b in its homologue, his genotype being heterozygous Fy^a Fy^b (see table 3). The phenotype frequencies in Caucasians are Fy (a+ b−) 0·1823, Fy (a+ b+) 0·4735, Fy (a− b+) 0·3302.[21]

Table 3 *Duffy blood group system (Fy)*

Phenotype	*Genotype*
Fy (a+ b+)	Fy^a Fy^b
Fy (a+ b−)	Fy^a Fy^a
Fy (a− b+)	Fy^b Fy^b

Results

Two type I families (figs 1, 2) gave positive scores for *Duffy*. One type II family (fig 3) showed two recombinants between the loci for *Fy* and *HMSN*. Other relevant details about these families are shown in tables 4 and 5. The lod scores for the various genetic markers tested have been published elsewhere.[12] Table 6 gives the sum of lod scores from the Bird *et al*[13 14] study and our study, establishing linkage between type I autosomal dominant *HMSN* and the *Fy* locus. As will be amplified in the

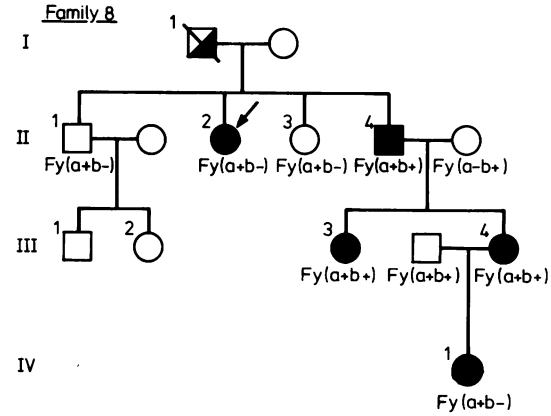

Fig 1 *Pedigree of autosomal dominant type I HMSN showing Duffy phenotypes. Filled symbols indicate affected individuals, half-filled symbol one presumed to be affected by history; propositus indicated by arrow.*

Table 4 *Summary of data in families with HMSN scoring for Duffy*

Family	*Type*	*Tested n*	*Generations n*	*Affected (n) Male*	*Female*
8	I	9	3	1	4
10	I	13	3	4	3
14	II	14	3	3	4
Total		36		8	11

Table 5 *Median nerve motor conduction velocity (MCV) in tested affected members of families with HMSN informative for Duffy*

	Family	*n*	*MCV (m s^{-1})*	
			Mean	*Range*
Type I	8	4	22·7	17–29
	10	7	21·7	12–30
Type II	14	6	44·8	36–58

Table 6 *Cumulative data establishing linkage between type I HMSN and the Fy locus*

	Recombination fraction, θ			
	0·1	*0·2*	*0·3*	*0·4*
Male lod scores				
Bird *et al*[13]	0·62	0·89	0·76	0·45
Present study	0·470	0·338	0·210	0·096
Female lod scores				
Bird *et al*[13]	1·68	1·06	0·54	0·22
Present study	0·255	0·204	1·146	0·079
Total	3·025*	2·492	1·656	0·845

*In a more recent paper, Bird *et al*[14] give slightly different lod scores bringing the cumulative total lod score to 3·022 at $\theta = 0{\cdot}1$.

Discussion, the cases examined by Bird *et al* can be accepted as HMSN type I.

ANALYSIS OF PEDIGREES

Family 8 (fig 1) is type I and clearly autosomal dominant. In generation II the proposita (II·2) and her affected brother (II·4) both have an Fy^a gene. II·4 who is heterozygous at the *Duffy* locus has transmitted the disease together with the Fy^a gene to his daughters III·3 and III·4. This gene could not have come from the mother as she is Fy (a− b+). Furthermore, III·4 has again transmitted the disease together with the Fy^a gene to her daughter IV·1. The latter is homozygous for the Fy^a gene so she must have received an Fy^a gene from each parent.

Family 10 (fig 2) is type I and also shows autosomal dominant inheritance. The affected female in generation II (II·1) is homozygous for the Fy^b gene. Hence all her children will be Fy (b+). Male III·2 who is heterozygous at the *Fy* locus has an unaffected child IV·1 who is Fy (a+ b−), that is, he is homozygous for the Fy^a gene and therefore the absence of disease in this family is associated with

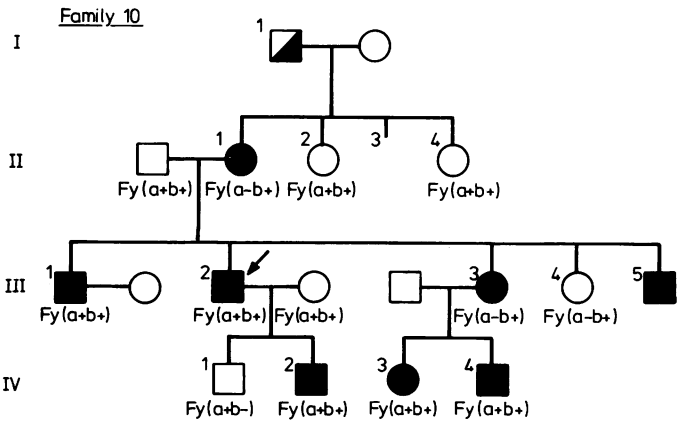

Fig 2 *Pedigree of autosomal dominant type I HMSN showing Duffy phenotypes. Symbols as in fig 1.*

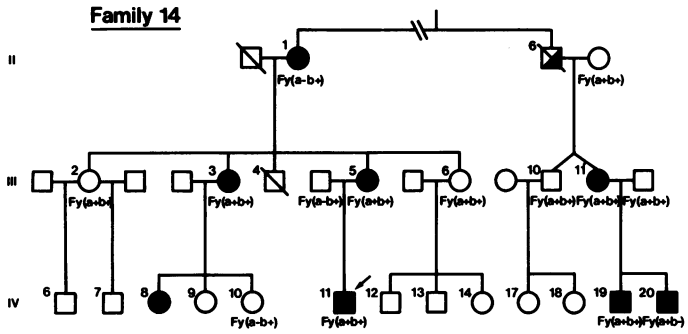

Fig 3 *Pedigree of autosomal dominant type II HMSN showing Duffy phenotypes. Symbols as in fig 1.*

the absence of the gene Fy^b. This is a nonrecombinant.

Family 14 (fig 3) is our only informative type II family. The pedigree also shows autosomal dominant inheritance. II·1 is homozygous for the Fy^b gene and must transmit an Fy^b gene to all her offspring in generation III. III·3 has inherited the disease and the Fy^b gene from her mother and passed it on to her unaffected daughter IV·10. The daughter is homozygous for the Fy^b gene and must have received one Fy^b gene from each parent. This is therefore a recombinant. Here type II *HMSN* and *Duffy* are not linked. III·5 again has inherited the disease and an Fy^b gene from her mother and she has an affected son IV·11 to whom she has failed to transmit the Fy^b gene. The Fy^b gene in IV·11 must have come from the father as he is homozygous for Fy^b and the Fy^a gene has come from the mother. This second recombinant again suggests that type II *HMSN* and *Duffy* are not linked.

Discussion

Whilst we were analysing our data, Bird *et al*[13] published their findings in a similar study of three families classifiable as autosomal dominant type I HMSN. Two were informative for the *Duffy* locus, comprising three and four generations and a total of 23 affected persons. At least one member of each of their families had an MCV of less than 20 m s^{-1} and one affected member in each informative family had hypertrophic changes on sural nerve biopsy.[14] Their lod scores were suggestive of linkage of autosomal dominant type I HMSN and the Duffy blood group genes. If we add our lod scores to those of Bird *et al* (table 6), a total lod score of 3·025 at 0·1 recombination fraction is reached, establishing linkage between the loci for autosomal dominant type I HMSN and the Duffy blood group. Neither Bird *et al* nor ourselves found evidence for linkage to other markers assigned to chromosome 1 (PGD, Rh and PGM-1; see tables 3 and 4).

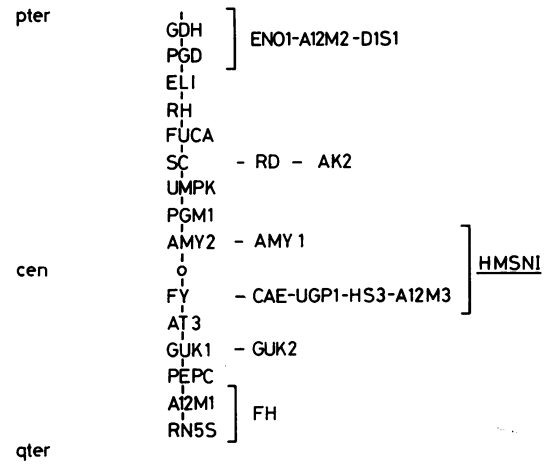

Fig 4 *Known genetic constitution of chromosome 1. Adapted from Cook and Hamerton.[24] Note that the Fy locus is on the long arm near the centromere (cen). The locus for autosomal dominant type I HMSN may be proximal or distal to Fy in relation to the centromere, that is nearer or more distant from AMY2 and AMY1.*

From the combined data of Bird *et al* and ourselves the locus for autosomal dominant type I HMSN has been confirmed as the 23rd locus definitely assigned to chromosome 1.[24] The *HMSN*/Duffy recombination fraction has been estimated to be of the order of 15%, that is, the distance between the two loci may be around 15 centimorgans.[24] Figs 4 and 5 show that the loci for *Fy* and autosomal dominant type I *HMSN* are thought to lie in the long arm of chromosome 1, near the centromere. In order to define further the position of the *HMSN* locus in relation to the *Duffy* locus, that is, whether the former is proximal or distal to the centromere in relation to the *Duffy* locus, it would be of value to test the families for amylase (Amy, see fig 4) and qh, which is a marker for the centromere.

The correlation coefficients obtained for median nerve motor conduction velocity between index

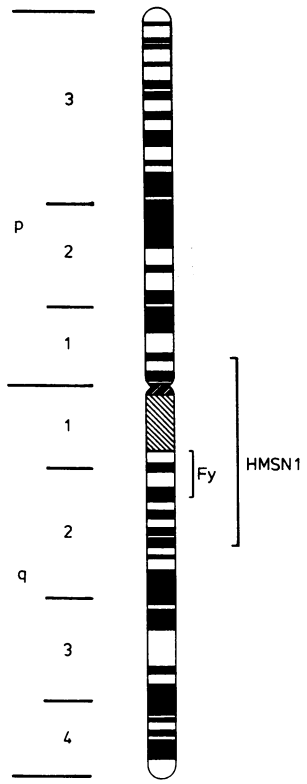

Fig 5 *Chromosome 1, adapted from ISCN.*[25] *Probable approximate regions for autosomal dominant type 1 HMSN and Fy loci are shown.*

cases and affected relatives with autosomal dominant type I HMSN suggest the existence of additional genetic heterogeneity.[3] Linkage studies on further families will therefore be of interest, although it is quite possible that multiple isoalleles at the same locus are involved.

Only one of our type II families was informative for *Duffy*. The two recombinants between *Duffy* and type II autosomal dominant *HMSN* suggest that these two loci are not linked and further support the hypothesis that there are at least two genetic variants of autosomal dominant HMSN. Further linkage studies in a larger number of type II families are now also required.

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Note added in proof: the previously published totals for cumulative data (reference 12, table 3) contain two errors. The total figures at recombinant fractions 0·2 and 0·3 should be 2·492 and 1·656 respectively, as stated in table 6 of this paper.