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LETTER

More evidence that founder effects exist in the European population

In 1996, the chemokine receptor CCR5 was shown to be involved in the process by which the human immunodeficiency virus (HIV) gains entry into $CD4^+$ lymphocytes.[1] Shortly after this discovery it was found that inheritance of a naturally occurring 32 base pair (bp) deletion in the receptor's gene (*CMKBR5*) significantly reduces the risk of infection in those exposed to HIV,[2] the deletion bearing allele (Δccr5) coding for a non-functioning protein.[2] These observations raised the possibility that chemokine receptor polymorphisms, such as Δccr5, might be important determinants in the development of other retroviral diseases. Although the environmental factor involved in the pathogenesis of multiple sclerosis is uncertain, a novel retrovirus is one candidate.[3] With this in mind, Bennetts *et al*[4] compared the frequency of the Δccr5 allele in Australian patients with multiple sclerosis and unrelated controls, but found no evidence for a protective effect. More recently, Libert *et al*[5] studied the Δccr5 allele in a variety of healthy European populations (not including the UK) and found a striking north–south gradient in allele frequency. In addition, these investigators identified strong linkage disequilibrium (LD) between Δccr5 and flanking microsatellite markers suggesting a founder effect with most, if not all, contemporary Δccr5 alleles originating from a single ancestral mutation event.[5]

In order to establish the role, if any, of Δccr5 in patients with multiple sclerosis from the United Kingdom we typed 185 simplex families (both parents and a single affected offspring). The Δccr5 allele frequency was 15.4% (57/370) in the 185 affected offspring, with genotype frequencies corresponding to those expected at Hardy Weinberg equilibrium. Transmission disequilibrium testing,[6,7] performed using the sibtdt program from the ASPEX package version 1.12, revealed no significant evidence for distorted transmission, with 48 Δccr5 alleles transmitted and 34 not transmitted (indicating a transmission rate in the 95% confidence interval 47.6%–69.4%). It should be noted, of course, that the modest sample size used in our study means that a small effect from Δccr5 cannot be excluded.

The flanking dinucleotide microsatellites used by Libert *et al* (D3S4579 and D3S4580) were also typed in these 185 families; phase of the alleles in each parent was inferred from those transmitted and thereby the frequency of each marker allele in both the Δccr5 bearing chromosomes ($n = 100$) and the wild type chromosomes ($n = 640$) was calculated (coincidentally the D3S4580 marker was found to have a low frequency null allele, of about 7%). Highly significant linkage disequilibrium was found between Δccr5 and the 138 bp allele of D3S4579, and between Δccr5 and the 144 bp allele of D3S4580 (see Table). These were confirmed as the same marker alleles found by Libert *et al* indicating that the UK Δccr5 alleles arose from the same common founder.

Although we have not found any evidence that Δccr5 is involved in determining susceptibility to multiple sclerosis, we confirm the findings of Libert *et al*. The existence of founder effects in large outbred populations (such as the Europeans) is a significant result in terms of polygenic disease. These data add to the growing evidence supporting the belief that LD frequently occurs in the region of disease genes. In monogenic diseases such as cystic fibrosis[8] the existence

Table Linkage disequilibrium with the Δccr5 allele

	Frequency of marker allele on parental chromosomes			
	Δccr5 % (n)	*Wild type* % (n)	χ^2	*P value*
138bp allele of D3S4579	88 (88)	6.3 (40)	404	7.3E–90
144bp allele of D3S4580	77 (77)	5.6 (36)	340	4.9E–76

The region of the 32 bp deletion in the *CCR5* gene was amplified using the primers TAG GTA CCT GGC TGT CGT CC and TTC CCG AGT AGC AGA TGA CC, the D3S4579 marker with primers AAG AGA TTG GTT CCA GGC ATG and CCG GAC CTT GCA TTA CAG GAC, and the D3S4580 marker with primers CCT TCT GGA GCA GCA CTT CCA and GTA AAT CTC CTA ACA ACA TGC. In each case the forward primer was fluorescently labelled and the genotyping was performed using the Applied Biosystems GENESCAN/GENOTYPER system.

of LD is well established, whilst in polygenic disease similar evidence is now beginning to emerge.[9]

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Jeremy Chataway, Stephen Sawcer, Robert Feakes, Francesca Coraddu, Simon Broadley, Julia Gray and Alastair Compston
University of Cambridge Neurology unit, Addenbrooke's Hospital, Cambridge, UKV

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