Island	Number of people	Number of individuals with respective genotype*						Frequency of mutant allele	
		wt/wt	*wt/m1*	*wt/m2*	*m1/m2*	*m1/m1*	*m2/m2*	*m1*	*m2*
Tanna	266	6	60	6	46	144	4	0·741	0·113
Malakula	227	6	49	18	49	103	2	0·670	0·156
Total observed	493	12	109	24	95	247	6	0·708§	0·133‡
Total estimated†	493	12	111	21	93	247	9‡		

*wt=wild type allele, *m1=CYP2C19m1* allele, *m2=CYP2C19m2* allele. †Calculated from the observed allele frequencies of *m1* and *m2*, in accordance with a Hardy-Weinberg equilibirum. §95% confidence interval=0·680 to 0·763. ‡95% confidence interval=0·112 to 0·154.

Frequencies of *CYP2C19* mutant alleles in two islands of Vanuatu

there are known racial differences in the frequencies of the PM phenotype: about 3% of whites and in 13–23% of orientals.[3] Poor metabolism results from a defect in the gene associated with the cytochrome P450 isoenzyme, *CYP2C19*. Two genetic defects, *m1* and *m2*, have been identified: the former accounts for 75–83% of the defective alleles in both white and Japanese PMs, while the latter was found only in Japanese.[4] We determined the distribution of the two *CYP2C19* mutations in two Vanuatu islands.

In March, 1996, malariometric surveys were conducted on Tanna and Malakula islands. The survey included finger prick sampling of blood for PCR from a capillary tube (75 μL) on to a filter paper. Dried filter-paper samples were collected from 493 people. DNA was extracted from a quarter of a dried blood spot. PCR was conducted as described by de Morais et al,[4] with PCR amplification of exon 5 followed by *Sma*1 digestion (*CYP2C19m1*) and amplification of exon 4 followed by *Bam*H1 digestion (*CYP2C19m2*).

The genotypes of the 493 villagers are shown in the table. Remarkably high frequencies of the two mutations were found. The overall frequency of the *m1* alleles was 0·708 (698/986), and that of the *m2* alleles was 0·133 (131/986). Only 145 individuals had at least one wild-type allele (*wt*). The observed genotype distribution corresponded well with those estimated from the allele frequencies of *CYP2C19m1* and *m2* in the study group, in accordance with a Hardy-Weinberg equilibrium (χ^2-test, $p>0·5$, power >99%). The population of Tanna Island showed higher frequency of *m1* and lower frequency of *m2* than that of Malakula Island ($p<0·05$).

In a separate study we correlated proguanil and cycloguanil concentration profiles in whole blood with genotypes in patients with malaria from the same area (unpublished). The results confirm that the genotyping predicted the phenotypes in all 20 patients tested. Thus, the data in the table suggest that 348 (70·6%) individuals have PM phenotype, which may have major implications for the efficacy of proguanil in this population. *CYP2C19* is also involved in the metabolism of other drugs such as imipramine, omeprazole, and diazepam.[3] Anthropological evidences suggest that Melanesians are of Mongoloid origin, and the ancestors of the people in Vanuatu may have migrated from Papua New Guinea about 4000 years ago.[5] Therefore, the finding of *m2* mutation in Vanuatu is not surprising. However the reasons for the high frequency of the *m1* allele are unclear.

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32 bp CCR-5 gene deletion and resistance to fast progression in HIV-1 infected heterozygotes

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Chemokine and AIDS research fields are converging. CCR-5 and fusin are receptors for chemokines which have been recently identified as co-receptors for HIV-1 infection. The CC-chemokines MIP-1α, MIP-1β, and Rantes bind to the CCR-5 receptor and can inhibit infection of target cells by HIV-1 monocytotropic strains.[1] A 32 base-pair deletion in the *CCR-5* gene (Δ32) is present in approximately 18% of white people, but virtually absent in black and Asian people. People homozygous for the Δ32 deletion are resistant to HIV infection.[2–4] Among heterozygotes, this deletion does not seem to confer resistance to HIV-1 infection. The role of the mutant CCR-5 allele in late disease progression is not yet clear.[4]

To gain insight into the role of CCR-5 in disease progression, we studied CCR-5 allele frequencies in HIV-1 infected individuals from the GRIV cohort which gathers blood samples from people in France characterised as either rapid or slow progressors. The GRIV cohort is the largest collection of blood samples from slow/fast progressors to-date (survey of more than 10 000 patients[5]). The people were selected by focusing on the extremes of clinical outcome in order to increase the significance of genetic analysis. Slow progressors were defined as HIV-infected people without symptoms for more than 8 years with CD4 cell count above 500×10^6/L in the absence of antiretroviral therapy. Fast progressors were those who had a CD4 cell count below 300×10^6/L less than 3 years after seroconversion.

With experimental methods previously published,[2] we evaluated the prevalence of the mutant allele of CCR-5 in 34 fast and 66 slow progressors. The prevalence of Δ32 deletion (heterozygous) among slow progressors was 24·3% (16/66) and among fast progressors was 2·9% (1/34). These results suggest that CCR-5 heterozygosity protects individuals from progression early after infection ($p<0·05$). The enrichment for the Δ32 allele among slow progressors (24% versus an expected 18% in the general white population) did not reach statistical significance. Of interest, the 16 heterozygous slow progressor individuals did not seem to have been preferentially infected by a specific route (hetero/homosexual, drug, transfusion).

CCR-5 heterozygosity confers a higher probability of non-progression during the first 3 years after seroconversion. Slow progressors have only a small increase in the frequency of CCR-5 heterozygosity relative to the general white population. This result can be easily biased due to the time period for non-progression selected or to genetic differences inherent in our cohort. A previous study of individuals infected by sexual transmission showed a maximum difference in disease progression between heterozygous and homozygous wild-type subjects between 10–12 years after seroconversion.[4]

These results are consistent with the proposed role of CCR-5 as the major co-receptor for HIV-1 monocytotropic strains which are known to be more prevalent in infected individuals early in disease. Relative to heterozygotes, individuals homozygous for the wild type allele could support increased levels of viral replication and therefore might progress more rapidly to AIDS. The presence of the mutant allele may prevent efficient HIV-1 replication by a reduction in the number of available receptors. This effect may be amplified by secondary increases in the level of antiviral chemokine secretion. A lack of significant protection late in disease might suggest the evolution of viruses toward the use of alternative co-receptors, such as fusin.

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Cluster of multiple sclerosis patients from Danish community

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Clusters are defined as geographically bounded groups of occurrence of a trait of sufficient size and concentration to be unlikely to have occurred by chance.[1] Clusters of multiple sclerosis (MS) outside families are viewed with sceptism by epidemiologists, but a Norwegian study showed that MS patients within the same birth cohort had lived closer to each other between 13 and 20 years of age than would be expected. The authors found the results compatible with the involvement of a common infectious agent, such as Epstein-Barr virus (EBV), acquired in adolescence.[2] Our group has searched for clusters of people who lived close together around puberty and who later developed MS. Besides a great number of couples we found six clusters in which three or more people had had close contact and later developed MS. Although it is uncertain how clusters should be interpreted, we report one in which eight people with verified MS originated from a small Danish community called Fjelsø.

Year of birth	Start of school	No of pupils starting school	No/sex of MS patients	Age at onset of disease
1945	1952	13	1/F	24
1946	1953	10	2/F,M	31,36
1947	1954	9	1/F	34*
1948	1955	14	0	. .
1949	1956	12	0	. .
1950	1957	13	0	. .
1951	1958	13	0	. .
1952	1959	12	1/F	38
1953	1960	9	1/M	35*
1954	1961	10	0	. .
1955	1962	12	1/M	30†
1956	1963	10	0	. .
1957	1964	8	1/F	37†

*The older one is maternal aunt to the younger one. †Siblings.

Year of birth and start of school for 145 pupils in elementary school at Fjelsø during 13-year period

All eight had lived within a 2·75 km^2 area (2·5 km×1·1 km), where 74 single-family houses, including some farms, were located. The community had a stable population with few migrations into and out of the area. During a 13-year period all the patients had for 7 years attended the same elementary school with 70–80 pupils. The school had 145 pupils during this period. All those who developed MS had been scouts together, with the older ones being scoutmasters for the younger ones and some of the older ones had also looked after the younger ones. Two cases were siblings and two were aunt and nephew, but MS had not been observed in any of the ancestors of the eight cases or among the school teachers. All cases of MS developed, at various ages and with variable courses, after the eight had left Fjelsø (table). None of the eight could recall symptoms of infectious mononucleosis.

The number of patients of the Fjelsø cluster is a third of that of the Faroe epidemic, which developed among more than 30 000 inhabitants during an 18-year period.[3] It is tempting to speculate that such a cluster may be due to one or more specific infectious agents. Our group has previously put forward a dual infection hypothesis for MS, suggesting that infection with a more or less widespread "MS retrovirus" is a prerequisite for development of MS, but MS develops only or especially in those who are infected with EBV around puberty or later in life and who are genetically susceptible.[4] Our research results support this hypothesis,[5] but further evidence is needed. If EBV is the initiating factor and/or is involved in the disease process in MS, one would expect that the same subtype of EBV will be found in more or all of the cluster members from the individual clusters, by contrast with what is seen in control cohorts. Studies are in progress to evaluate this further.

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