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Manuscript submitted March 5, 2002, and accepted in revised form July 12, 2002.

A Founder Effect in the Hyperimmunoglobulinemia D and Periodic Fever Syndrome

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Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS; *Mendelian Inheritance in Man* [MIM] 260920) is an autosomal, recessively inherited disorder characterized by recurrent episodes of fever, abdominal distress, arthralgia, and aphthous ulcers (1). In addition to the constantly elevated immunoglobulin D (IgD) levels, all patients have a marked acute phase response during the febrile attacks. First described as a separate syndrome in The Netherlands (2), the disease was identified later in patients from other European countries such as France (3–6), the United Kingdom (7), Germany (8,9), Italy (10,11), Turkey (12), and the Czech Republic (13), as well as the United States (14) and Japan (15).

Many HIDS patients have mutations in the gene for mevalonate kinase (16–18) that cause decreased activity. Mevalonate kinase is an essential enzyme in the isoprenoid pathway that produces cholesterol, dolichol, and ubiquinone, as well as causes protein isoprenylation (19). How deficient enzyme activity causes the clinical phenotype is unknown. At least 18 mutations have been described; they are distributed throughout almost all coding regions of the gene (19–21). One mutation, which leads to a replacement of valine by isoleucine (V377I), was present in about 80% (36/45) of HIDS patients who were unrelated (20,22). Most HIDS patients

are compound heterozygotes, which means that they have a combination of two different mutations in the mevalonate kinase gene. The combination is usually a V377I mutation with a I268T (isoleucine to threonine) mutation.

The clustering of reported cases in The Netherlands and in western Europe, most notably of those with a V377I mutation, is remarkable (Figure 1). To gain insight into the ancestral origin of the mutation, and to explain the geographical distribution of HIDS, we performed an extensive haplotype study using five closely linked markers surrounding the mevalonate kinase gene in 14 families with HIDS.

METHODS

Patients

Patients were selected from the Nijmegen International HIDS registry, which was set up in 1992. It includes clinical and laboratory data on 188 HIDS patients (23). All patients had recurrent attacks of fever ($\geq 38.5^\circ\text{C}$) with an acute phase response, an elevated serum IgD level (> 100 U/mL) measured on two occasions at least 1 month apart, and one or more of the following symptoms during attacks: lymphadenopathy, abdominal distress, skin manifestations, arthralgia or arthritis, and splenomegaly.

We identified 16 families with one or more affected siblings with HIDS and known mevalonate kinase genotype. Fourteen families were informative enough to allow haplotype analysis (Figure 2); they originate from The Netherlands (seven families), France (two families), the United Kingdom (two families), Spain (one family), Czech Republic (one family), and Italy (one family). We also included 4 patients (3 from The Netherlands, 1 from the United States) who were homozygous for the V377I mutation. Clinical details and results from genotype analysis of these patients and families have been described (20,24,25). Analysis of mevalonate kinase genotype in the 14 families yielded 11 V377I alleles, seven I268T alleles, and 10 alleles with other mevalonate kinase mutations (P167L, H20P, H20N, R215Q, two deletions, and four unknown). The control alleles were gathered from unaffected members within the same families, to ensure that they would originate from the same population. The study was carried out after informed consent was obtained from all subjects and after formal approval was given by the Medical Ethical Committee of the University Medical Center Nijmegen, The Netherlands.

Markers

Genomic deoxyribonucleic acid (DNA) was extracted from whole blood or Epstein-Barr virus-transformed lymphoblastoid cell lines using standard procedures. Five markers were used for the haplotype analysis: D12S1605, D12S1339, D12S1645, D12S234, and D12S1583 (26).

Primer sequences were obtained from the Genome Database. The markers were amplified using a standard polymerase chain reaction method. The marker allele sizes were analyzed with an ABI PRISM 310 Genetic Analyzer (PE Applied Biosystems, Foster City, California). Using the Basic Local Alignment Search Tool (BLAST) (27), the exact position of the mevalonate kinase gene and markers D12S1339, D12S1645, and D12S234 could be determined within two overlapping DNA sequences deposited in the Genome Database (AC007623 and AC007570). We determined that the HIDS gene is located between markers D12S1645 and D12S234.

Linkage Disequilibrium Analysis

Linkage disequilibrium indicates an association between a genetic marker and a disease-associated mutation, and is a measure for cosegregation of a specific haplotype with a mutation in a population. Chi-squared tests were used to compare the frequency of the associated numbered marker allele on chromosomes carrying the V377I mutation with the frequency on normal chromosomes. Linkage disequilibrium was assessed by the formula $\delta = (P_D - P_N)/(1 - P_N)$, where P_D is the frequency of the associated marker allele on disease chromosomes and P_N is the frequency of the same marker allele on normal chromosomes (28).

RESULTS

Base-pair sizes of the different alleles of the five markers, and their frequency in the control alleles, are shown in Table 1. There were 11 definite V377I haplotypes in the 14 families, and the haplotype 3-1-4-8 was conserved among persons carrying the V377I mutation (Figure 3). This haplotype of at least the two flanking markers was also found on all of the V377I alleles of the 4 patients homozygous for this mutation, except on one allele of one Dutch patient. There was significant linkage disequilibrium for this haplotype (Table 2), and the 3-1-4-8 haplotype was not seen on any of the V377I-negative control alleles, indicating that it is highly mutation associated and consistent with a founder effect.

Seven alleles with the I268T mutation in the mevalonate kinase gene could be collected from the 14 families. Allele 6 of marker D12S234 was only found in association with the I268T mutation and not in any of the 25 control alleles or in any of the alleles with other mutations in the mevalonate kinase gene. This again suggests a founder effect, although the results were not statistically significant.

If the V377I allele is in Hardy-Weinberg equilibrium, and based on the estimate that there are 30 families in The Netherlands with that allele, the overall frequency of the allele in The Netherlands is about 0.3%.

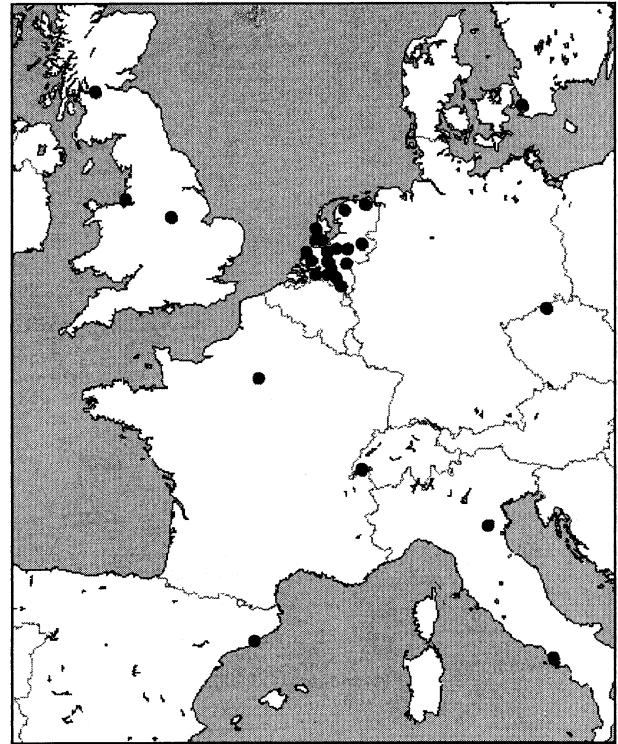


Figure 1. Geographical distribution of 32 patients or families with at least one allele with a base-pair change 1129G → A in the mevalonate kinase gene, leading to replacement of valine at codon 377 by isoleucine (V377I). Cases, represented by black dots, cluster in The Netherlands. Not shown: 1 patient in Turkey, 2 patients in the United States.

DISCUSSION

The high prevalence of the V377I mutation among HIDS patients from different families inferred a founder effect with a common ancestor, and the geographical clustering of HIDS seemed to support this assumption. Conversely, the large number of HIDS patients of Dutch origin might reflect reporting bias due to awareness of the disorder, and because measurement of IgD levels is included in the diagnostic work-up of patients with periodic fever in The Netherlands (29).

We constructed haplotypes surrounding the mevalonate kinase gene in HIDS patients from seven different countries. Our results show that the majority of V377I alleles that we studied share a common ancestral haplotype, indicating that most carriers of the V377I mutation share the same ancestor. As most V377I mutation-positive HIDS patients live in The Netherlands, it could be speculated that the founder also lived there, although formal proof is lacking.

Familial Mediterranean fever (MIM 249100), another autosomal, recessive, periodic fever syndrome that has

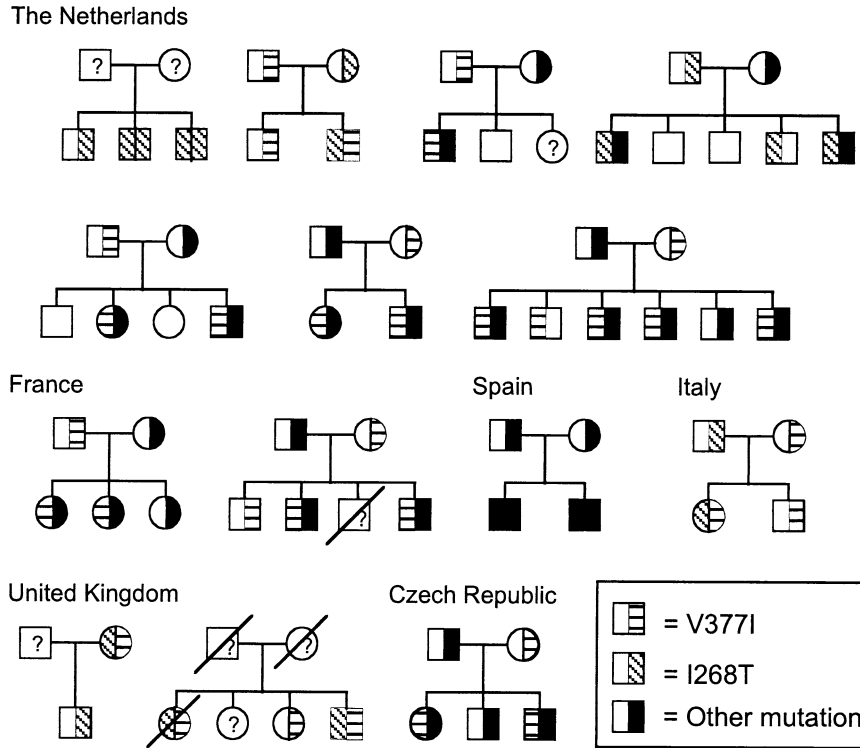


Figure 2. Pedigrees of 14 families with one or more siblings with hyperimmunoglobulinemia D and periodic fever syndrome who were included in this study. The occurrence of the V377I mutation, the I268T mutation, or an allele with a different mutation in the mevalonate kinase gene, is indicated. A question mark denotes a family member who was not available for genetic analysis.

phenotypic similarities to HIDS, is caused by mutations in the pyrin gene (1). A founder effect has also been established for this disorder (30,31). In contrast with HIDS, the carrier frequency of mutations in the pyrin gene may be as high as 14% in selected populations (31). The high frequency of pyrin mutations might be explained by a survival advantage of heterozygotes (carriers of one pyrin mutation) (30). Heterozygous carriers of a pyrin mutation have elevated concentrations of acute phase proteins,

perhaps indicating a primed inflammatory response that is beneficial for responding to infections, thus leading to better survival (32,33). The spread of the mutation might also be explained by random genetic drift and migration.

In conclusion, we found that the most common mutation in HIDS, the V377I mutation, originates from a common ancestral haplotype in most families. The founder of this haplotype and the V377I mutation most likely lived in The Netherlands, and the mutation spread

Table 1. Base-Pair Sizes of the Numbered Alleles of the Five Markers and Their Frequency in the Control Alleles

	D12S1605 (n = 23)		D12S1339 (n = 15)		D12S1645 (n = 25)		D12S234 (n = 25)		D12S1583 (n = 24)	
	Base-Pair Size (kb)	Number (%)	Base-Pair Size (kb)	Number (%)	Base-Pair Size (kb)	Number (%)	Base-Pair Size (kb)	Number (%)	Base-Pair Size (kb)	Number (%)
1	194	3 (13)	262	0	209	5 (20)	310	3 (12)	220	1 (4)
2	196	1 (4)	264	4 (27)	211	1 (4)	315	4 (16)	224	11 (46)
3	198	14 (61)	266	2 (13)	213	7 (28)	317	10 (40)	234	2 (8)
4	200	4 (17)	268	4 (27)	215	1 (4)	321	5 (20)	237	2 (8)
5	202	1 (4)	270	2 (13)	228	1 (4)	323	2 (8)	239	3 (13)
6			272	0	230	2 (8)	325	0	241	2 (8)
7			274	0	238	4 (16)	319	1 (4)	243	1 (4)
8			276	3 (20)	240	1 (4)			245	1 (4)
9					242	1 (4)			247	1 (4)
10					244	2 (8)			249	0

kb = kilobase.

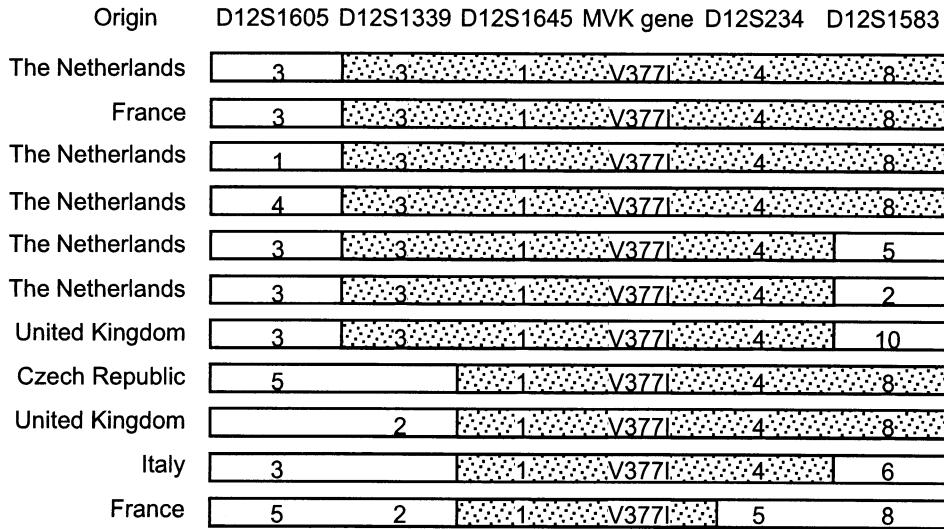


Figure 3. The haplotypes of 11 alleles from the families carrying the V377I mutation, analyzed for the indicated markers. Numbers indicate different marker alleles; see Table 1 for base-pair sizes. The common mutation-related haplotype (3-1-4-8) is marked by the shaded area. Missing numbers represent missing data.

from there to the rest of Europe and the United States. This study underscores the importance of establishing the ethnic background of patients in the differential diagnosis of periodic fever syndromes.

ACKNOWLEDGMENT

The technical assistance of Willy Nilissen, Joop Theelen, and Saskia van der Velde-Visser is gratefully acknowledged. We thank the patients and families for their cooperation. The following members of the International HIDS Study Group supplied data and samples used in this study: R. J. Powell (Nottingham, United Kingdom), C. M. R. Weemaes (Nijmegen, The Netherlands), T. Espanol (Barcelona, Spain), A. Metton

(Thonon les Bains, France), C. D. A. Stehouwer (Amsterdam, The Netherlands), A. M. Prieur (Paris, France), A. M. Farrell (Glasgow, United Kingdom), D. Kastner (Bethesda, Maryland), L. Businco (Rome, Italy), U. Saatci (Ankara, Turkey), R. Tamminga (Groningen, The Netherlands), and D. Jilek (Usti nad labem, Czech Republic).

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Table 2. Analysis of Linkage Disequilibrium of the V377I-Linked Haplotype

Marker	Allele	Distance*	Linkage Disequilibrium Analysis			
			P _D	P _N	P Value [†]	δ
D12S1605	3		0.64	0.61	0.84	0.09
D12S1339	3	33.5	0.73	0.14	0.003	0.68
D12S1645	1	4.5	0.95	0.20	<0.001	0.93
D12S234	4	39.8	0.68	0.20	0.001	0.61
D12S1583	8		0.53	0.04	<0.001	0.51

* Distance of markers in kilobases, relative to mevalonate kinase gene.

† By chi-squared analysis.

P_D = frequency of the allele on chromosomes with 1129G → A base-pair change in mevalonate kinase gene; P_N = frequency of the allele on normal chromosomes; δ = measure for allele-specific association, calculated as (P_D - P_N)/(1 - P_N), where δ = 0 asserts no association and δ = 1.0 represents complete association of the genetic marker with the mutated chromosome.

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Dr. Simon is a recipient of a Dutch Scientific Research Fellowship for Clinical Investigators (KWO 920-03-116). Dr. Drenth is an Investigator of the Royal Netherlands Academy of Arts and Sciences.

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Manuscript submitted April 3, 2002, and accepted in revised form July 12, 2002.