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New Mutations of *CIAS1* That Are Responsible for Muckle-Wells Syndrome and Familial Cold Urticaria: A Novel Mutation Underlies Both Syndromes

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Mutations of *CIAS1* have recently been shown to underlie familial cold urticaria (FCU) and Muckle-Wells syndrome (MWS), in three families and one family, respectively. These rare autosomal dominant diseases are both characterized by recurrent inflammatory crises that start in childhood and that are generally associated with fever, arthralgia, and urticaria. The presence of sensorineural deafness that occurs later in life is characteristic of MWS. Amyloidosis of the amyloidosis-associated type is the main complication of MWS and is sometimes associated with FCU. In FCU, cold exposure is the triggering factor of the inflammatory crisis. We identified *CIAS1* mutations, all located in exon 3, in nine unrelated families with MWS and in three unrelated families with FCU, originating from France, England, and Algeria. Five mutations—namely, R260W, D303N, T348M, A439T, and G569R—were novel. The R260W mutation was identified in two families with MWS and in two families with FCU, of different ethnic origins, thereby demonstrating that a single *CIAS1* mutation may cause both syndromes. This result indicates that modifier genes are involved in determining either a MWS or a FCU phenotype. The finding of the G569R mutation in an asymptomatic individual further emphasizes the importance of such modifier a gene (or genes) in determining the disease phenotype. Identification of this gene (or these genes) is likely to have significant therapeutic implications for these severe diseases.

Introduction

Muckle-Wells syndrome (MWS [MIM 191900]) and familial cold urticaria (FCU [MIM 120100]) belong to the group of hereditary fever syndromes that includes familial Mediterranean fever (FMF [MIM 249100]), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS [MIM 260920]), and tumor necrosis factor receptor 1–associated periodic syndrome (TRAPS [MIM 142680 and MIM 134610]) (Delpech and Grateau 2001; Drenth and Van der Meer 2001). MWS and FCU are rare autosomal dominant disorders reported in the northern-European population. The first clinical signs occur during childhood and generally include fever, joint inflammation, myalgias, urticaria, and conjunctivitis (Kile and Rusk 1940; Muckle and Wells 1962). In MWS, a progressive sensorineural deafness occurs later in life, and a renal amyloidosis of the amyloidosis associated (AA) type can sometimes be observed (Messier et al. 1988). In contrast, FCU is defined by a highly specific clinical feature: the effect of cold on the skin, which triggers the general symptoms of inflammatory crises (Hoffman et al. 2001*b*). MWS and FCU have both been localized to chromosomal region 1q44 (Cuisset et al. 1999; Hoffman et al. 2000). Recently, Hoffman et al. (2001*a*) identified missense mutations in the *CIAS1* gene, which cosegregated in three families with FCU and in one family with MWS. The gene is expressed in peripheral blood leukocytes and encodes a protein called "cryopyrin," which contains several distinct motifs, including a pyrin domain (also found in the marenostrin/

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Table 1

List of Families Affected with MWS or FCU

Family	Syndrome	Nationality	Reference
1	MWS	French	Lagrue et al. 1972
2	MWS	French	Prost et al. 1976; Barrière et al. 1977
3	FCU	French	Present study
4	FCU	Algerian	Present study
5	MWS	English	Watts et al. 1994
6	MWS	French	Hedon et al. 1983
7	MWS	French	Present study
8	MWS	French	Present study
9	MWS	French	Present study
10	MWS	English	Present study
11	MWS	French	Present study
12	FCU	French	Bader-Meunier et al. 1996

pyrin encoded by the *MEFV* gene involved in FMF [Masumoto et al. 2001]), a central nucleotide-binding site (NACHT subfamily; for explanation of the "NACHT" acronym, see the "Discussion" section) domain in exon 3, and a C-terminal domain containing seven leucin-rich repeats (LRR). Recently, it has been demonstrated that cryopyrin selectively interacts with apoptosis-associated specklike protein containing a CARD domain (ASC) and that ASC linked to cryopyrin activates nuclear factor κB (NF-κB) (Manji et al. 2002).

In this article, we present five new mutations, all located in exon 3 of *CIAS1,* in 12 families with MWS or FCU. Of these 12 families with MWS, 3 were previously studied for the localization of MWS to the 1q44 chromosomal region (Cuisset et al. 1999).

Patients, Material, and Methods

Patients

Mutations in the *CIAS1* gene were searched in 12 unrelated families with MWS or FCU (table 1). Pedigrees are shown in figure 1. Each participant was examined and provided informed written consent. Studies of some members of these families have been published elsewhere. Patients presented characteristic clinical signs, such as urticaria, arthralgia, arthritis, fever, ocular signs, and AA amyloidosis. The presence of sensorineural deafness allowed us to ascertain MWS and to exclude FCU (Muckle 1979), whereas the triggering effect of cold was characteristic of FCU.

Mutation Detection

Peripheral blood was obtained from patients, and DNA was extracted as described elsewhere (Cuisset et al. 1999). A mutation search was performed on genomic DNA after PCR amplification of the nine exons of the *CIAS1* gene, through use of oligonucleotides and experimental conditions described by Hoffman et al. (2001*a*). Free nucleotides and oligonucleotides were eliminated by exonuclease I (10 units) (USB) and shrimp alkaline phosphatase (1 unit) (USB) treatment at 37°C for 15 min, followed by incubation at 80°C for 15 min. Mutation detection was performed by fluorescent sequencing with dye-terminator chemistry (Perkin Elmer) on a 3100 automated sequencer (ABI Perkin Elmer).

The R260W mutation was analyzed in the control population by PCR amplification of genomic DNA, through use of the forward primer MWS-R260W-5′ (5′-GACCCCGATGATGAGCATTCT-3′) and the reverse modified primer MWS-R260W-3′ (5′-TCTCACAAGG-CTCACCTCTC-3′). The PCR products were digested with the restriction enzyme *Taq*I, which revealed the presence of the R260W mutation. The other novel mutations (T348M, D303N, G569R, and A439T) either abolished or created a restriction site (table 2). This was used to test the frequency in control population.

Microsatellite Analysis

Genotyping of the *CIAS1* gene chromosomal region was performed with the following eight markers: AFMB358wg1, D1S423, AFMA274zc5, AFMB005wh9, D1S2836, D1S2215, AFM142wx1, and D1S2682. We performed PCR and automated fluorescent genotyping using standard procedures, as described elsewhere (Cuisset et al. 1999).

Single-Nucleotide Polymorphism (SNP) Analysis

The analysis of the sequences allowed us to identify four SNPs located in exon 3 of the *CIAS1* gene. These SNPs are localized on the third base of codons 219 (C/T), 242 (A/G), 260 (A/G), and 434 (C/T), and they do not modify the encoded amino acid. The frequency of each allele in the control population is given in table 3.

Table 2

***CIAS1* Mutations Found in Families with MWS and FCU**

Family	Nucleotide Change	Amino Acid Change	Enzyme-Site Change	Control Frequency
1–4	C778T	R260W	*Taq*I(+)[a]	0/134
5–8	C1043T	T348M	*Nla*III(+)	0/146
9	G907A	D303N	*Taq*I(−)	0/138
10	G1705C	G569R	*Aci*I(+)	0/122
11	G1315A	A439T	*Aci*I(−)	0/122
12	G562A	V198M	…[b]	…[b]

[a] PCR was performed using modified oligonucleotides (see "Patients, Material, and Methods" section).

[b] See Hoffmann et al. (2001*a*).

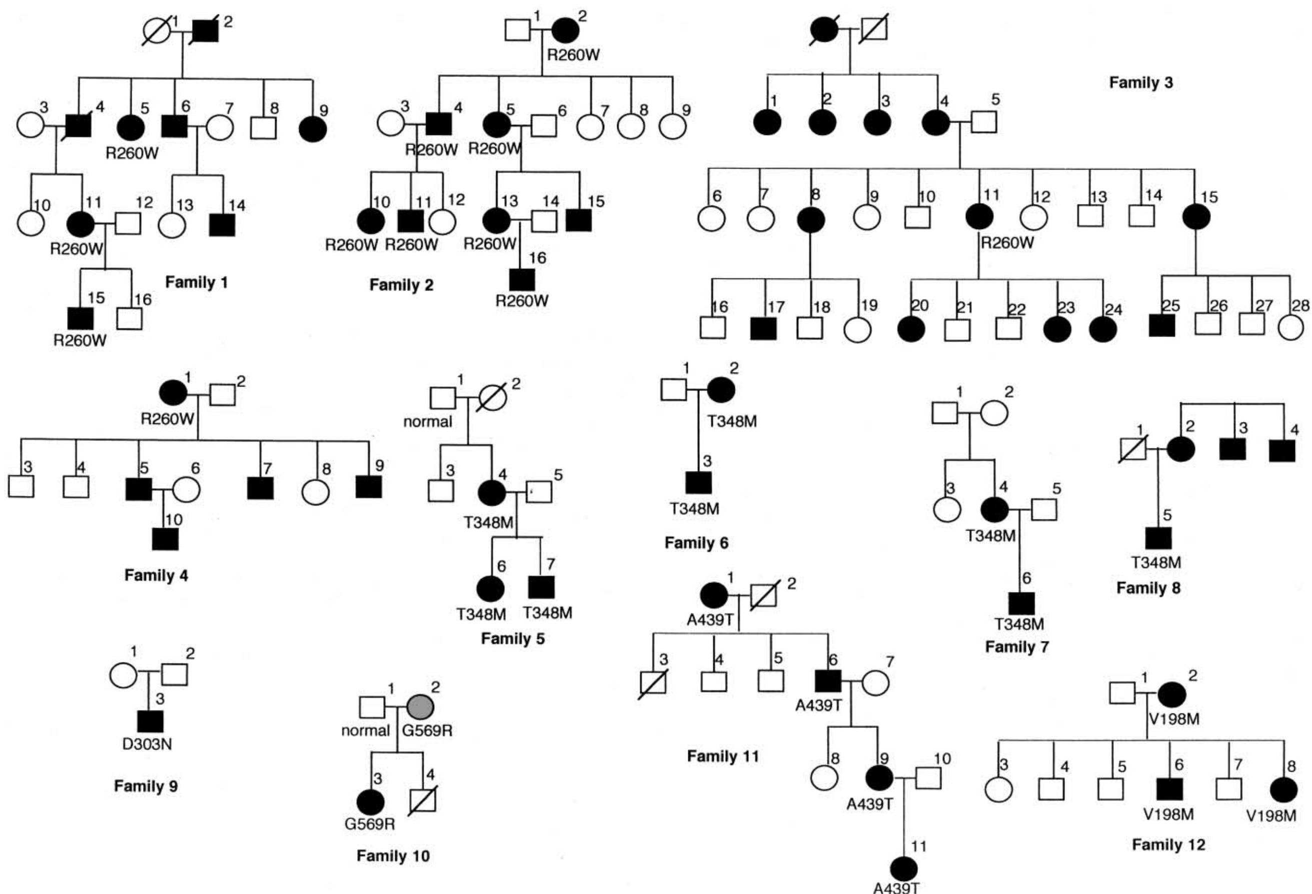

Figure 1 Pedigree of the 12 families with MWS or FCU, with mutation analysis of *CIAS1*. Affected individuals are shown as blackened circles (females) or blackened squares (males). Deceased individuals are denoted by diagonal slashes. A gray circle represents an asymptomatic individual carrying an MWS mutation.

Results

CIAS1 *Mutation Analysis*

A total of 12 families, including 9 with MWS and 3 with FCU, were studied (table 1). The nine unrelated families with MWS include three families previously reported to show linkage to the 1q44 region (Cuisset et al. 1999), as well as four French and two English families with a high suspicion of MWS. The three families with FCU included one Algerian and two French families. Genealogical trees are shown in figure 1. The main clinical signs of patients are summarized in table 4. Among these families, we identified a total of six mutations, all located in exon 3 of the *CIAS1* gene; five of these are novel mutations and were not present in the control population (table 2). The R260W and T348M mutations are the main ones encountered in families 1–4 and in families 5–8, respectively (fig. 2). This R260W mutation was found in two families with MWS and in two families with FCU. In families 1–3, the disease segregated over four generations. Study of families 1, 2, and 5 had previously allowed us to localize MWS to the 1q44 chromosomal region (Cuisset et al. 1999). Patients in these families exhibited clinical features of the syndrome. AA amyloidosis was diagnosed by renal biopsy in family 1 (Messier et al. 1988). In families 3, 4, and 12, the patients had FCU with urticaria, arthralgia, and fever, since infancy. The inflammatory crisis in patient 11 of family 3 started after cold exposure. The triggering effect of

Table 3

***CIAS1* SNPs Identified in the Present Study**

Nucleotide Change	Codon	% (No.) of Alleles in the Unaffected Population
C/T	219	92.5 (37) C, 7.5 (3) T
A/G	242	45 (18) A, 55 (22) G
A/G	260	10 (4) A, 90 (36) G
C/T	434	5 (2) C, 95 (36) T

Table 4

Main Clinical Signs of Patients with MWS and FCU

Family and Patient (Sex)	Mutation	Age (years)	Age at Onset[a] (years)	Urticaria	Deafness	Articular Signs	Ocular Signs	Fever	Proteinuria	Renal AA Amyloidosis
1:										
5 (F)	R260W	?	?	+	−	+	−	−	+	+
11 (F)	R260W	42	B	+	+	+	+	−	?	?
15 (M)	R260W	14	3	+	−	−	+	−	?	?
2:										
2 (F)	R260W	84	?	+	+	+	+	−	?	?
4 (M)	R260W	60	I	+	+	+	+	−	?	?
5 (F)	R260W	60	I	+	+	+	+	−	?	?
10 (F)	R260W	36	10	+	+	+	+	−	?	?
11 (M)	R260W	34	I	+	+	+	+	−	+	?
13 (F)	R260W	39	I	+	+	+	+	−	?	?
16 (M)	R260W	12	3	+	−	+	+	−	?	?
3:										
11 (F)	R260W	53	1	+	−	+	?	+	?	?
4:										
1 (F)	R260W	53	I	+	−	+	?	+	?	?
5:										
4 (F)	T348M	57	2	+	+	+	+	+	?	?
6 (F)	T348M	31	B	+	+	+	+	+	?	?
7 (M)	T348M	28	B	+	+	+	+	+	?	?
6:										
2 (F)	T348M	57	?	+	+	+	?	−	?	?
3 (M)	T348M	30	?	+	+	+	+	+	?	?
7:										
4 (F)	T348M	47	?	+	+	+	+	+	?	?
6 (M)	T348M	9	?	+	+	+	+	+	?	?
8:										
5 (M)	T348M	41	3	+	+	+	+	−	?	?
9:										
3 (M)	D303N	?	B	+	+	+	?	−	?	?
10:										
3 (F)	G569R	31	B	+	+	+	+	−	?	?
11:										
6 (M)	A439T	?	?	+	+	+	+	−	?	?
9 (F)	A439T	36	3	+	+	−	+	−	?	?
11 (F)	A439T	7	2	+	?	−	+	−	?	?
12:										
2 (F)	V198M	40	1	+	−	+	−	+	?	?
6 (M)	V198M	13	B	+	−	+	−	+	?	?
12 (F)	V198M	4	B	+	+	−	−	−	?	?

NOTE.—? = unknown; + = present; − = absent.
[a] B = at birth; I = in infancy.

cold was not observed in patients from families 4 and 12. Both parents of patient 1 of family 4 were from Algeria. In these three families, the disease was clearly dominantly inherited.

Families 5–8 with MWS displayed the same T348M mutation. In contrast to families with the R260W mutation, families with the T348M mutation are small. Inheritance of this mutation is found only in a two-generation family. No renal AA amyloidosis was associated with this mutation.

The D303N mutation was found in a single patient, who presented with all clinical criteria of MWS. Since the parents of this patient have no mutation, D303N can be considered to be a de novo mutation in this family.

In family 10, patient 3 is the only one affected by MWS. His mother, patient 2, shares the same mutation, but, so far, she has not developed clinical signs of MWS. The G569R mutation seems to be inherited with a low penetrance. In family 11, MWS is due to a new mutation, A439T, through four generations. Another mutation at the same codon, A439V, has been characterized previously in a family with FCU, which suggests the presence of a mutational hotspot in this region (Hoffman et al. 2001*a*). Patients from family 12 had FCU and carried

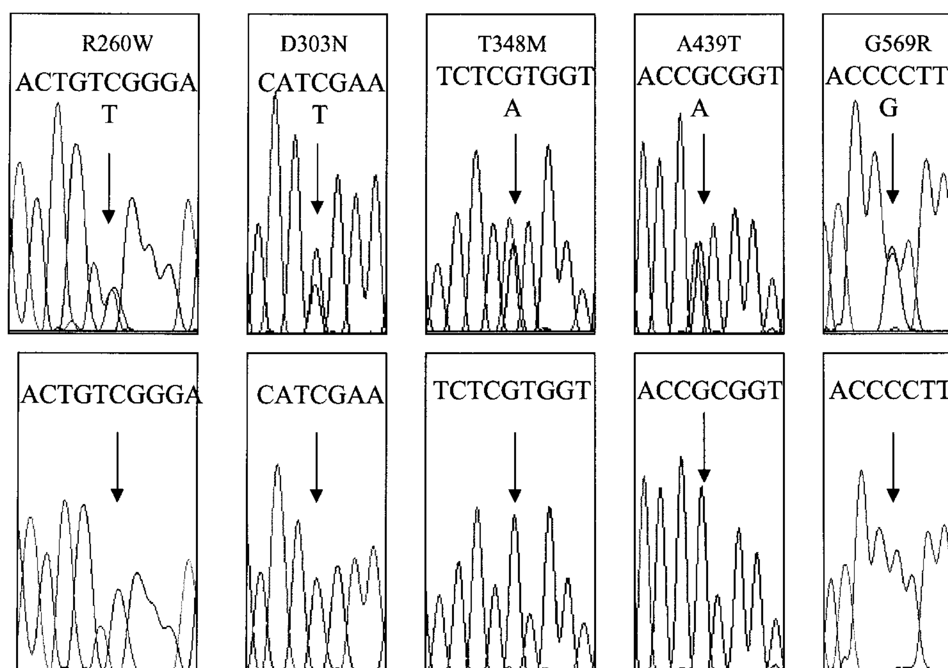

Figure 2 DNA-sequence electrophoregrams for the five novel *CIAS1* mutations identified in the present study. Upper electrophoregrams correspond to the patients, lower ones to the control. Arrows indicate the position of the mutation. Sequences showing mutations R260W and A439T are on the coding strand, and D303N, T348M, and G569R are on the opposite strand.

the V198M mutation, which was previously described in a family with FCU (Hoffman et al. 2001*a*).

Haplotype Analysis

Do unrelated patients with the same R260W or T348M mutation share common haplotypes? Sequencing of the *CIAS1* gene in patients with MWS or FCU allowed us to characterize several SNPs (table 3). We evaluated the frequency of these SNPs in the control population. We then used these intragenic SNPs and microsatellites to construct haplotypes in families 1–8. We did not find a common founder microsatellite haplotype for the R260W or T348M mutations, which suggests that these mutations appear on different alleles (fig. 3 and table 5).

Discussion

The role of *CIAS1* in MWS and FCU was originally discerned on the basis of different missense mutations found in three families with FCU and in only one family with MWS (Hoffmann et al. 2001*a*). The present study presents the largest series of families and novel mutations reported since the discovery of the *CIAS1* gene and confirms its involvement in MWS and FCU. This is the first demonstration that MWS and FCU can be due to the

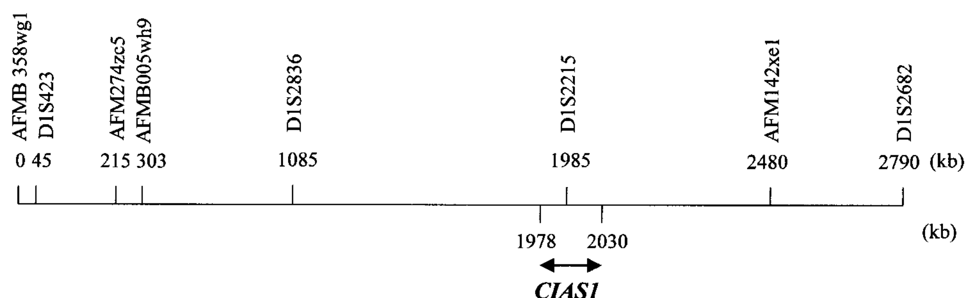

Figure 3 Physical map of the region surrounding the *CIAS1* gene, between microsatellite markers AFMB358wg1 and D1S2682 (UCSC Human Genome Project Working Draft).

Table 5

Genotypes and Haplotypes of Patients with MWS and FCU Carrying the R260W and T348M Mutations

Family and Patient	Genotype													
	AFMB358wg1	D1S423	AFM274zc5	AFMB005wh9	D1S2836	D1S2215	T219T (C/G)	A242A (A/G)	R260W	R260R (A/G)	T348M	S434S (C/T)	AFM142xe1	D1S2682
1:														
5	2/2	1/2	3/5	2/2	1/4	1/2	C/C	A/G	R260W	G/G	…	C/T	3/3	4/9
11	2/3	1/1	3/7	2/2	1/1	2/3	C/C	G/G	R260W	G/G	…	C/C	3/3	4/4
15	2/2	1/2	3/4	2/2	1/1	2/3	C/C	A/G	R260W	G/G	…	…	2/3	1/4
Haplotype	***2***	***1***	***3***	***2***	***1***	***2***	***C***	***G***	***R260W***	***G***	…	***C***	***3***	***4***
2:														
2	1/2	2/2	1/5	1/2	2/3	2/3	C/T	G/G	R260W	G/G	…	…	1/4	1/4
4	1/2	2/2	1/7	1/1	2/6	2/3	C/C	A/G	R260W	G/G	…	…	1/3	4/4
5	1/2	2/2	1/7	1/1	2/6	2/3	C/C	A/G	R260W	G/G	…	C/C	1/3	4/4
10	1/2	1/2	1/6	1/2	1/2	2/3	C/C	A/G	R260W	G/G	…	…	1/1	1/4
11	1/2	1/2	1/6	1/2	1/2	2/3	C/C	A/G	R260W	G/G	…	C/C	1/1	1/4
13	1/2	2/2	1/8	1/2	1/2	2/3	C/C	G/G	R260W	G/G	…	…	1/1	2/4
16	1/2	2/2	1/2	1/3	2/4	2/3	C/C	G/G	R260W	G/G	…	…	1/3	4/4
Haplotype	***1***	***2***	***1***	***1***	***2***	***2***	***C***	***G***	***R260W***	***G***	…	***C***	***1***	***4***
5:														
4	2/2	1/2	2/3	1/2	1/6	3/?	C/C	A/A	…	G/G	T348M	C/C	3/4	3/4
6	2/3	2/2	1/3	1/2	4/6	3/3	C/C	A/A	…	G/G	T348M	C/C	1/4	4/4
7	2/2	1/2	2/3	1/2	4/6	3/3	C/C	A/A	…	G/G	T348M	…	1/4	4/4
Haplotype	***2***	***2***	***3***	***1***	***6***	***3***	***C***	***A***	…	***G***	***T348M***	***C***	***4***	***4***
6:														
2	2/2	3/5	5/9	1/5	9/10	3/3	…	…	…	…	T348M	…	3/3	3/4
3	2/2	3/7	9/11	1/2	9/10	3/3	C/C	G/G	…	G/G	T348M	C/C	3/3	3/3
Haplotype	***2***	***3***	***9***	***1***	***9***	***3***	***C***	***G***		***G***	***T348M***	***C***	***3***	***3***
3:														
11	…	…	…	…	…	…	C/C	A/G	R260W	G/G	…	…	…	…
4:														
1	…	…	…	…	…	…	C/C	G/G	R260W	A/G	…	C/C	…	…
7:														
6	…	…	…	…	…	…	C/T	G/G	…	G/G	T348M	C/C	…	…
8:														
5	…	…	…	…	…	…	C/C	A/G	…	A/G	T348M	C	…	…

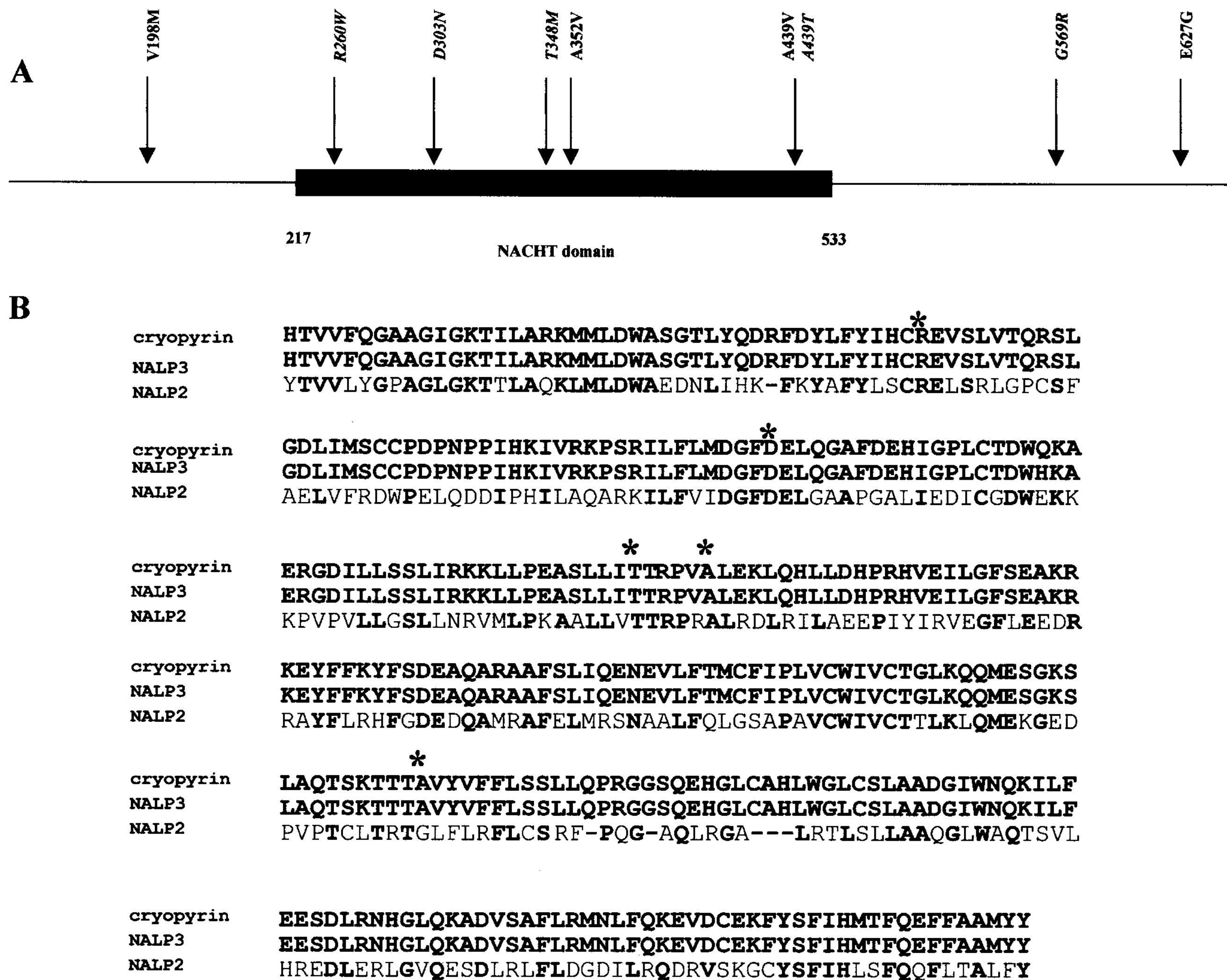

Figure 4 *A,* Exon 3 of *CIAS1* (GenBank accession number AF427617). The blackened box represents the NACHT domain, and all mutations involved in MWS and FCU are shown. Mutations in italics are those described in the present study. *B,* Alignment of the NACHT-domain amino acid sequence from human cryopyrin, *NALP2,* and *NALP3* (GenBank accession numbers AAG30289 and AF418985). Asterisks (*) represent positions of mutations in the NACHT domain. Amimo acid homologies are represented by boldface characters.

same mutation, R260W, implying that MWS and FCU are in fact the same syndrome, in which some clinical signs, such as deafness, AA amyloidosis, and cold sensitivity, are not always present. This strongly suggests that mutations in *CIAS1* do not account for a unique genetic contribution and that unknown modifier genes can influence the phenotype. This observation has already been made in patients with FMF who carry the characteristic clinical signs and the same genotype but who do not always develop AA amyloidosis. The presence of AA amyloidosis is highly influenced by the presence of polymorphisms in the *SAA1* gene (Cazeneuve et al. 2000). A similar observation in rheumatoid arthritis has shown that polymorphisms in the *SAA1* promoter may influence the development of AA amyloidosis (Booth et al. 1998; Moriguchi et al. 1999, 2001). The clinical signs of MWS and FCU seem to be more pronounced than expected, since, in families 3 and 4, which had recurrent febrile urticaria, the triggering effect of cold and sensorineural deafness were absent. These two families are similar to an Indian family described by McDermott et al. (2000), which presented with incomplete clinical signs of MWS and FCU and showed linkage to the same region. The spectrum of diseases associated with *CIAS1* mutations is thus not restricted to MWS and FCU and will probably include some forms of familial inflammatory urticaria that, so far, have no genetic explanation.

Several families in the present study displayed the same mutation—families 1–4 (R260W) and families

5–8 (T348M)—and therefore the question of a common origin can be raised. We studied microsatellites and biallelic polymorphisms in the patients carrying the same mutation. No common haplotypes based on microsatellites were found for these two mutations. The haplotype analysis covers a 2.9-Mb region, including the *CIAS1* gene, which is probably too large to allow us to observe a common origin, especially if the mutations are ancient. On the basis of SNP analysis, we did not observe significant haplotypes for the R260W mutation. Unfortunately, it was not possible to obtain genomic DNA from different patients of families 3 and 4. The R260W mutation is carried in families who do not share a common ethnic origin. Until now, MWS and FCU had been reported only in northern-European populations; however, family 4 is from Algeria, which enlarges the ethnic spectrum. We therefore suspect that the R260W mutation appears on different chromosomes. Among families 5–8, which share the same common T348M mutation, preliminary results of SNP study seem to indicate that the T348M mutation appeared on different chromosomes.

At this time, all mutations in both syndromes are missense mutations located in exon 3 of the *CIAS1* gene and mainly involve the NACHT domain (fig. 4). The "NACHT" family acronym was recently used by Koonin and Aravind (2001) and is based on the following protein names: NAIP (neuronal apoptosis inhibitor protein), CIIA (MHC class II transcription activator CIITA), HET-E (bacterial nucleotide triphosphatase protein) and TP1 (telomerase-associated protein). The existence of this new family was assessed with the identification of a new proapoptotic protein—CARD4, which contains a nucleotide triphosphatase protein—that has a highly significant sequence similarity to CIITA and that activates NF-κB. The role of the NACHT domain is not actually known, but mutations in genes encoding a NACHT domain have recently been found to be involved in inflammatory diseases such as Blau syndrome and Crohn disease (Hugot et al. 2001; Miceli-Richard et al. 2001; Ogura et al. 2001). The highest degree of homology between NACHT domains has been found between cryopyrin, NALP2, and NALP3 (fig. 4). Mutations observed in cryopyrin are located on amino acids conserved among these three proteins. Of the 14 mutations responsible for MWS and FCU, 12 described so far consist of the replacement of either a cytosine by a thymine or a guanine by an adenine. This suggests that exon 3 of *CIAS1* contains several mutational hotspots, and it supports the hypothesis that deamination of methylcytosines in CpG sites represents one major mechanism underlying the occurrence of MWS and FCU. This hypothesis could allow us to clarify several points: (1) two de novo mutations were found in four families (Hoffman et al. 2001*a*); (2) transmission of the disease phenotype was associated with the T348M mutation only over two generations; and (3) high mutability of two codons was observed—codon 439, where two different mutations, A439T and A439V, were found (GCG→ACG [present study] and GCG→GTG [Hoffman et al. 2001*a*], respectively), and codon 260, where a R260W mutation (CGG→TGG) and a frequent polymorphism (CGG→CGA) were observed.

Discovery of involvement of the *CIAS1* gene in MWS and in FCU confirms the genetic heterogeneity of dominantly inherited forms of recurrent fevers. The clinical spectrum of diseases associated with *CIAS1* mutations is not limited to MWS and FCU and includes another form of familial urticaria, which does not meet the clinical criteria for MWS and FCU. The new diagnostic test will help in the clinical diagnosis and management of the conditions in patients affected with inflammatory recurrent syndromes, including those who belong to an ethnic group known to be at risk for FMF.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *CIAS1* [accession number AF427617], *NALP2* [accession number AAG30289], and *NALP3* [accession number AF418985])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for MWS [MIM 191900], FCU [MIM 120100], FMF [MIM 249100], HIDS [MIM 260920], and TRAPS [MIM 142680 and MIM 134610])

UCSC Human Genome Project Working Draft, http://genome.cse.ucsc.edu/

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