

## Molecular Analysis of the Mevalonate Kinase Gene in a Cohort of Patients with the Hyper-IgD and Periodic Fever Syndrome: Its Application as a Diagnostic Tool

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**Background:** The hyper-IgD and periodic fever syndrome (HIDS) is characterized by recurrent attacks of fever, abdominal distress, and arthralgia and is caused by mevalonate kinase mutations.

**Objective:** To ascertain the role of mevalonate kinase and the usefulness of molecular diagnosis in HIDS.

**Design:** Cross-sectional study.

**Setting:** The international Nijmegen HIDS registry.

**Patients:** 54 patients from 41 families who met the clinical criteria for HIDS.

**Measurements:** Clinical symptoms and signs, immunoglobulin concentration, leukocyte count, erythrocyte sedimentation rate, mutation analysis, and mevalonate kinase enzyme activity assay.

**Results:** There were two groups of patients: 41 patients with mevalonate kinase mutations (classic-type HIDS) and 13 patients without mutations (variant-type HIDS). Patients with classic-type HIDS had a lower mevalonate kinase enzyme activity, a higher IgD level, and more additional symptoms with attacks. The IgD level did not correlate with disease severity, mevalonate kinase enzyme activity, or genotype.

**Conclusion:** Genetic heterogeneity exists among patients with a clinical diagnosis of HIDS.

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Periodic fever encompasses a group of disorders characterized by limited periods of fever that recur for years in otherwise healthy persons. These fevers are highly discouraging and frustrating for physicians and patients alike because elaborate clinical investigations frequently fail to substantiate the diagnosis (1, 2). Over the past few years, several distinct subtypes of periodic fever have emerged (3–7), one of which is the hyper-IgD and periodic fever syndrome (HIDS) (8).

Patients with HIDS experience recurrent episodes of high fever accompanied by lymphadenopathy, abdominal distress, and arthralgia (9, 10); the episodes last several days and recur every few weeks. Most patients are from western Europe, but patients have also been identified in the United States (11). In patients with HIDS, levels of serum IgD are constantly elevated. The diagnosis is based on clinical grounds and elevated serum IgD levels but requires a high index of suspicion.

Two studies that used different genetic methods established that mutations in mevalonate kinase cause HIDS (12, 13). Early in the process of cholesterol synthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase catalyzes the production of mevalonic acid, which is then phosphorylated by the enzyme

mevalonate kinase. One study searched the genome by using blood samples from members of affected HIDS families and established linkage with the locus for mevalonate kinase (12). Another study detected minor elevated urinary excretions of mevalonic acid and an impaired mevalonate kinase activity in a patient with HIDS (13). Each study independently discovered disease-associated mutations in the mevalonate kinase gene in affected patients.

To ascertain the role of mevalonate kinase in HIDS, we searched for mutations in the gene and examined the enzyme activity of mevalonate kinase in 54 patients with the typical clinical and laboratory features of HIDS.

### METHODS

#### Patients

Patients were selected on the basis of previous inclusion in the Nijmegen HIDS registry, an international database that includes data on 176 patients (9), and availability of DNA and lymphoblast cell lines. All patients met the following criteria: repeated episodes of fever (body temperature > 38.5 °C) with biochemical evidence of an acute-phase response, including elevated

erythrocyte sedimentation rate and leukocytosis; a constantly elevated serum IgD level ( $>100$  kIU/mL), as measured on two occasions; and one or more of the following symptoms during attacks—lymphadenopathy, abdominal distress (vomiting, diarrhea, pain), skin lesions (erythematous macules and papules), arthralgia, or splenomegaly.

We enrolled 54 patients from 41 families and 12 unaffected parents of patients. Our sample included patients of Dutch ( $n = 42$ ), French ( $n = 4$ ), British ( $n = 2$ ), Czech ( $n = 2$ ), Spanish ( $n = 2$ ), Belgian ( $n = 1$ ), and Turkish ( $n = 1$ ) nationality. Patients and family members underwent a thorough clinical examination during and between attacks. Blood samples were collected during and between fever episodes; laboratory results are from samples taken during remissions unless otherwise indicated. The medical ethical committee of the University Medical Center St. Radboud, Nijmegen, the Netherlands, formally approved this study. All patients gave informed consent for participation in the study.

### Screening of Mutations in the Mevalonate Kinase Gene

Immortalized lymphoblast cell lines were generated by in vitro infection of lymphocytes by Epstein–Barr virus. These cell lines were used to extract ribonucleic acid, and complementary DNA was produced by using standard techniques. The complete coding region of the mevalonate kinase gene was amplified by performing polymerase chain reactions, and mutations were detected by using fluorescent sequencing, as described elsewhere (12, 14).

### Mevalonate Kinase Enzyme Analysis

Mevalonate kinase enzyme activity was determined in 36 of the 54 patients with HIDS and 12 parents of patients with classic HIDS who are (obligate) heterozygous for the mevalonate kinase mutation. We employed a radiometric assay by using extracts of cultured lymphocytes from Epstein–Barr immortalized cell lines, as described elsewhere (15, 16).

### Statistical Analysis

We performed statistical analyses by using the chi-square test, the unpaired nonparametric Mann–Whitney U test, and nonparametric Spearman correlation co-

efficients. Analyses were performed by using GraphPad Prism software, version 3.02 for Windows (GraphPad Software, Inc., San Diego, California). The significance level, the probability of a type I error, was set at 0.05.

## RESULTS

### Mutation Analysis

Mutation analysis revealed mutations in the gene for mevalonate kinase in 41 of the 54 tested patients, as described elsewhere (12, 14). We detected a missense mutation—a 1–base pair exchange in the gene resulting in an amino acid change in the protein—in 64 of 82 examined alleles. A deletion of a small number of base pairs was detected in 5 alleles, and RNA was absent from 7 alleles. The pertinent mutation could not be determined in 6 alleles. Thirty-seven of the 41 patients with gene mutations were compound heterozygotes, which means they possess a different mutation on each allele of the gene.

Despite exhibiting the clinical phenotype of HIDS and completely fulfilling the clinical criteria, 13 of the 54 patients had no detectable mutation of the mevalonate kinase gene. To detect whether mutations in the mevalonate kinase gene result in a different clinical picture, we separated our cohort into two groups: We designated patients with HIDS who met the clinical criteria for HIDS and carried mutations in the mevalonate kinase gene as having classic-type HIDS and designated the mutation-negative patients who met the clinical criteria for HIDS as having variant-type HIDS.

### Mevalonate Kinase Enzyme Activity

The top part of the **Figure** shows the mevalonate kinase enzyme activity in individual patients with HIDS. The mean enzyme activity ( $\pm$ SD) in patients with classic-type HIDS ( $0.42 \pm 0.25$  nmol/min per mg of protein) was greatly depressed compared with that of patients who had variant-type HIDS ( $2.8 \pm 1.3$  nmol/min per mg of protein) ( $P < 0.001$ ). In both groups, no significant correlations were found between enzyme activity and clinical disease severity, as measured in number of febrile days per year ( $r = 0.06$  [ $P > 0.2$ ] for classic-type HIDS;  $r = -0.15$  [ $P > 0.2$ ] for variant-type HIDS), or between enzyme activity and IgD levels ( $r = 0.02$  for classic-type vs.  $r = -0.11$  for variant-type [ $P > 0.2$  for both comparisons]). Participants who had

children with classic-type HIDS and who were heterozygous for the mevalonate kinase mutation had a mean enzyme activity ( $1.7 \pm 0.77$  nmol/min per mg of protein) that was lower than that of patients who had variant-type HIDS ( $P = 0.008$ ) but was significantly higher than that of their affected offspring ( $P < 0.001$ ).

### Clinical Phenotype and Laboratory Values

The Table depicts the pertinent clinical variables in the classic-type and variant-type HIDS groups. Age at onset of febrile attacks was greater in patients with variant-type HIDS. Compared with patients who had classic-type HIDS, patients with variant-type HIDS tended to have longer attacks (mean duration,  $6.9 \pm 5.7$  days for variant-type vs.  $4.7 \pm 1.7$  days for classic-type) and longer attack-free intervals (mean duration,  $9.3 \pm 9.2$

weeks for variant-type vs.  $5.6 \pm 3.8$  weeks for classic-type), although these differences were not statistically significant ( $P > 0.2$  for both comparisons). Of the 13 patients with variant-type HIDS, 1 patient had a brother and mother with similar symptoms, and 1 patient had an affected brother and daughter. As shown in the Table, patients with classic-type HIDS were more likely to have several types of accompanying symptoms.

The intensity of the acute-phase response during attacks was greater in patients with classic-type HIDS, as evidenced by a significantly higher erythrocyte sedimentation rate (Table).

### Laboratory Values

Levels of IgA and IgG<sub>3</sub> were higher and IgG<sub>4</sub> values were lower in patients with classic-type HIDS than in

**Table. Characteristics of Patients with Classic-Type or Variant-Type Hyper-IgD and Periodic Fever Syndrome\***

Variable	Patients with Classic-Type HIDS (n = 41)	Patients with Variant-Type HIDS (n = 13)	P Value
Clinical feature			
Mean age, y	31.2	30.3	–
Men/Women, n/n	24/17	8/5	–
Mean duration of attack (shortest, longest), d	4.0, 5.4	6, 7.8	–
Mean attack-free interval (shortest, longest), wk	4.8, 6.5	8.7, 10.5	–
Median age at onset (range), mo	3 (0–120)	24 (0–636)	0.02†
Mean laboratory value $\pm$ SD			
Maximum IgD level, kIU/L	1168.8 $\pm$ 1090.3	311.8 $\pm$ 143.9	<0.001†
IgA level, g/L	5.37 $\pm$ 2.75	2.66 $\pm$ 0.82	0.001†
IgG level, g/L	12.7 $\pm$ 3.6	13.9 $\pm$ 5.1	
IgG <sub>1</sub> level, g/L	8.6 $\pm$ 2.4	7.9 $\pm$ 3.2	
IgG <sub>2</sub> level, g/L	2.0 $\pm$ 0.9	2.6 $\pm$ 1.5	
IgG <sub>3</sub> level, g/L	1.2 $\pm$ 0.7	0.5 $\pm$ 0.1	<0.001†
IgG <sub>4</sub> level, g/L	0.2 $\pm$ 0.2	0.5 $\pm$ 0.4	0.009†
IgM level, g/L	1.4 $\pm$ 0.9	1.5 $\pm$ 0.8	
Erythrocyte sedimentation rate, mm/h‡	92.2 $\pm$ 29.3	63.5 $\pm$ 35.3	0.02†
Leukocyte count, $\times 10^9$ cells/L‡	17.8 $\pm$ 7.2	14.4 $\pm$ 6.0	
Symptom, n (%)			
Attack after immunization	7 (100)	2 (33)	<0.001§
Vomiting	36 (88)	4 (31)	<0.001§
Diarrhea	28 (68)	4 (31)	<0.001§
Lymphadenopathy	40 (98)	7 (54)	<0.001§
Splenomegaly	20 (49)	2 (15)	<0.001§
Skin lesions	35 (85)	8 (62)	<0.001§
Arthritis	29 (71)	6 (46)	<0.001§
Serositis	5 (12)	0 (0)	<0.001§
Abdominal pain	34 (83)	8 (62)	<0.001§
Arthralgia	36 (88)	9 (69)	0.011§
Aphthous ulcers	4 (67)	2 (50)	0.015§
Cold chills	31 (76)	10 (77)	–
Headache	26 (63)	8 (62)	–

\* HIDS = the hyper-IgD and periodic fever syndrome.

† Calculated by using the Mann–Whitney U test.

‡ Measured during a fever episode.

§ Calculated by using the chi-square test.

|| Not unequivocally known in all patients. Information on attacks after immunizations was obtained from 7 and 6 patients with classic-type and variant-type HIDS, respectively, and on aphthous ulcers from 6 and 4 patients.

patients with variant-type HIDS. Although both groups of patients had high serum levels of IgD, the levels in patients with classic-type HIDS greatly exceeded those in patients with variant-type HIDS (Figure, bottom). However, in two affected siblings of separate patients with classic-type HIDS, we detected low values of IgD, although both patients carried the same mutations, had typical HIDS attacks, and had depressed activity of the mevalonate kinase enzyme similar to that seen in their affected sibling. Furthermore, no significant correlation was found between level of IgD and mevalonate kinase enzyme activity or between IgD levels and the number of febrile days per year ( $r = 0.05$  [ $P > 0.2$ ] in classic-type;  $r = 0.46$  [ $P = 0.11$ ] in variant-type).

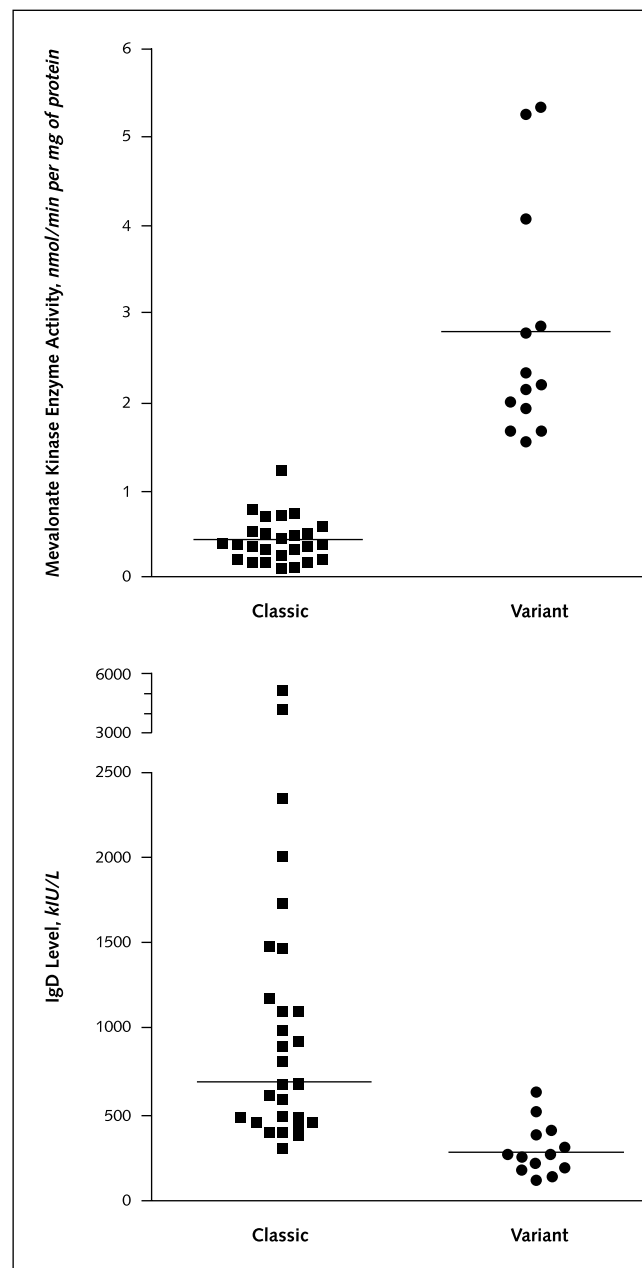
## DISCUSSION

Recent efforts in localization and positional cloning identified mevalonate kinase as the causative gene in HIDS (12, 13). This enabled us to develop and evaluate a molecular genetic test of the mevalonate kinase gene as a diagnostic tool for HIDS. We detected disease-associated mutations in 76% of patients in a cohort of 54 patients. Most patients were compound heterozygotes, which means that they carried a different mutation on each allele of the mevalonate kinase gene. The mutations had clear physiologic consequences, such as considerably decreased activity of the enzyme mevalonate kinase in cultured lymphoblasts.

We could delineate a substantial subgroup (24%) of our patient sample who had the typical clinical presentation of HIDS but lacked mutations in the mevalonate kinase gene. This suggests that there is genetic heterogeneity among patients with clinical symptoms of HIDS. Although we did not rule out the possibility of mutations in the promotor or intronic sequences or the possible occurrence of very large deletions, these scenarios are unlikely because the patients had normal mevalonate kinase enzyme activity.

To establish any distinctive features apart from mutations in the mevalonate kinase gene, we examined the two subgroups. Patients with HIDS who showed mutations in the gene for mevalonate kinase were denoted as having classic-type HIDS, and patients who carried no mutation in this gene were designated as having variant-type HIDS. Subtle differences in symptoms, signs, and laboratory values could be detected (Table). In general,

**Figure.** Mevalonate kinase enzyme activity and IgD levels in patients with classic-type or variant-type hyper-IgD and periodic fever syndrome (HIDS).



**Top.** Mevalonate kinase enzyme activity, as measured in lymphoblasts, in patients with classic-type (squares) and variant-type (circles) HIDS. The horizontal bars represent the mean. **Bottom.** Serum level of IgD in patients with classic-type versus variant-type HIDS. Horizontal bars represent the median of the groups. Normal range in healthy persons for serum IgD level is  $<100$  kIU/L.

patients with classic-type HIDS were younger at first attack, tended to have shorter but more frequent febrile attacks, and had more additional symptoms during attacks. Although patients with the variant type had high IgD and IgA levels, their values were lower than those seen in patients with the classic type. Intriguingly, most of the patients with variant-type HIDS had a negative family history, suggesting that the occurrence of the variant type is sporadic. The early onset of symptoms, however, suggests a genetic predisposition.

Given their phenotypic similarities, the patients with the variant type and patients with the classic type of HIDS may share a common inflammatory pathway distal of mevalonate kinase that results in the febrile attacks. Earlier studies indicated the activation of cytokines during fever attacks in HIDS (17, 18), suggesting the involvement of macrophage activation. However, it is unclear how a single enzyme defect in the isoprenoid pathway gives rise to an inflammatory disorder such as HIDS. Some insight might be gained from evaluation of inhibitors of HMG-CoA reductase, the enzyme that produces the substrate for mevalonate kinase. These drugs not only decrease cholesterol level but also have anti-inflammatory properties (19). The anti-inflammatory effects of HMG-CoA reductase inhibitors seem contradictory to the proinflammatory phenotype of HIDS, which is caused by an enzyme defect one step downstream from HMG-CoA reductase.

Our study also raises questions about the significance of IgD in the pathophysiology of HIDS. The height of serum IgD levels could not be related to clinical disease severity. Although IgD levels in patients with variant-type HIDS were lower than those in patients with classic-type HIDS, both groups had considerably elevated IgD levels. This finding suggests that high IgD values do not result directly from mutated mevalonate kinase. Houten and colleagues' study (13) suggests that patients with periodic fever who do not have increased IgD levels may also have mutations in mevalonate kinase. We previously demonstrated that symptoms in HIDS may antedate the increase in serum IgD level in childhood (9, 20). These findings might suggest that IgD acts as a secondary marker that can be found in most, but not all, patients with HIDS. Still, we think that measurement of IgD levels in patients with periodic fever is valuable. If a patient has early onset of symptoms (before the end of the first year of life), has a sibling with

periodic fever, and has an elevated IgD level, the results of the current study indicate that the patient probably has classic-type HIDS.

We propose to diagnose HIDS by using previously established clinical criteria (9). By use of a genetic diagnostic tool, patients with HIDS can then be assigned to one of two groups on the basis of having (classic type) or lacking (variant type) mutations in the gene for mevalonate kinase. Patients with classic-type HIDS are a relatively homogeneous group with a predictable inheritance pattern and clinical presentation, which can facilitate the counseling of individual patients.

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