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Linkage of Familial Hemophagocytic Lymphohistiocytosis to 10q21-22 and Evidence for Heterogeneity

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Summary

Familial hemophagocytic lymphohistiocytosis (FHL) is an autosomal recessive disorder characterized by the early onset of overwhelming activation of T lymphocytes and macrophages, invariably leading to death, in the absence of allogeneic bone marrow transplantation. Using genomewide genetic linkage analysis, we analyzed a group of 17 families with FHL and mapped a locus for FHL to the proximal region of the long arm of chromosome 10. Ten families showed no recombination with three tightly linked markers, D10S1650 (LOD score [*Z*]=6.99), D10S556 (*Z*=5.40), and D10S206 (*Z*=3.24), with a maximum multipoint LOD score of 11.22 at the D10S1650 locus. Haplotype analysis of these 10 families allowed us to establish D10S206 and D10S1665 as the telomeric and the centromeric flanking markers, respectively. Heterogeneity analysis and haplotype inspection of the remaining families confirmed that in seven families FHL was not linked to the 10q21-22 region, thus providing evidence for genetic heterogeneity of this condition.

Introduction

Familial hemophagocytic lymphohistiocytosis (FHL; MIM 267700), also known as "familial hemophagocytic reticulosis," "familial histiocytic reticulosis," "familial erythrophagocytic lymphohistiocytosis," or "familial histocytosis," is a fatal inherited inflammatory disorder occurring during infancy or early childhood (Farquhar and Claireaux 1952; Henter et al. 1998). It is inherited as an autosomal recessive disease with an estimated frequency, in Sweden, of 1 child/50,000 live births (Henter et al. 1991*b*). FHL is one of the so-called hemophagocytic lymphohistiocytosis (HLH) syndromes, which are characterized by hyperactivation and proliferation of T cells and macrophages, associated with fever, edema, hepatosplenomegaly, pancytopenia, coagulation abnormality, liver dysfunction, and features of hemophagocytosis in bone marrow, lymph nodes, spleen, and liver (Arico et al. 1996; Henter et al. 1998). In addition, CNS involvement is frequent in these syndromes, with manifestations ranging from confusion to severe seizures and neurological impairment (Haddad et al. 1997). These clinical characteristics are associated with the overproduction, by T lymphocytes and macrophages, of several cytokines, including interferon-γ (INFγ), and tumor necrosis factor–α (Henter et al. 1991*a*). Chemotherapy and immunosuppressive treatment are transiently effective (Stéphan et al. 1993), but FHL is invariably lethal unless treated by bone marrow transplantation (Baker et al. 1997; Jabado et al. 1997). The primary cause of this condition remains unknown.

Other causes of inherited HLH have been reported—for example, Chédiak-Higashi syndrome (MIM 214500) (Bejaoui et al. 1989; Nagle et al. 1996; Barbosa et al. 1997) and Griscelli syndrome (MIM 214450) (Griscelli et al. 1978; Pastural et al. 1997), both associated with partial albinism, and X-linked lymphoproliferative syndrome (XLP; MIM 308240) (Purtilo et al. 1975; Coffey et al. 1998; Sayos et al. 1998). Acquired forms of HLH can also occur, associated with infections (Risdall et al. 1979), autoimmune diseases, histiocytosis X, or malignancies (Writing Group of the Histiocyte Society 1987; Jaffe et al. 1993). Acquired HLH, however, usually occurs later in childhood. Diagnosis of FHL thus depends on the association of both positive and negative criteria, including the early occurrence and se-

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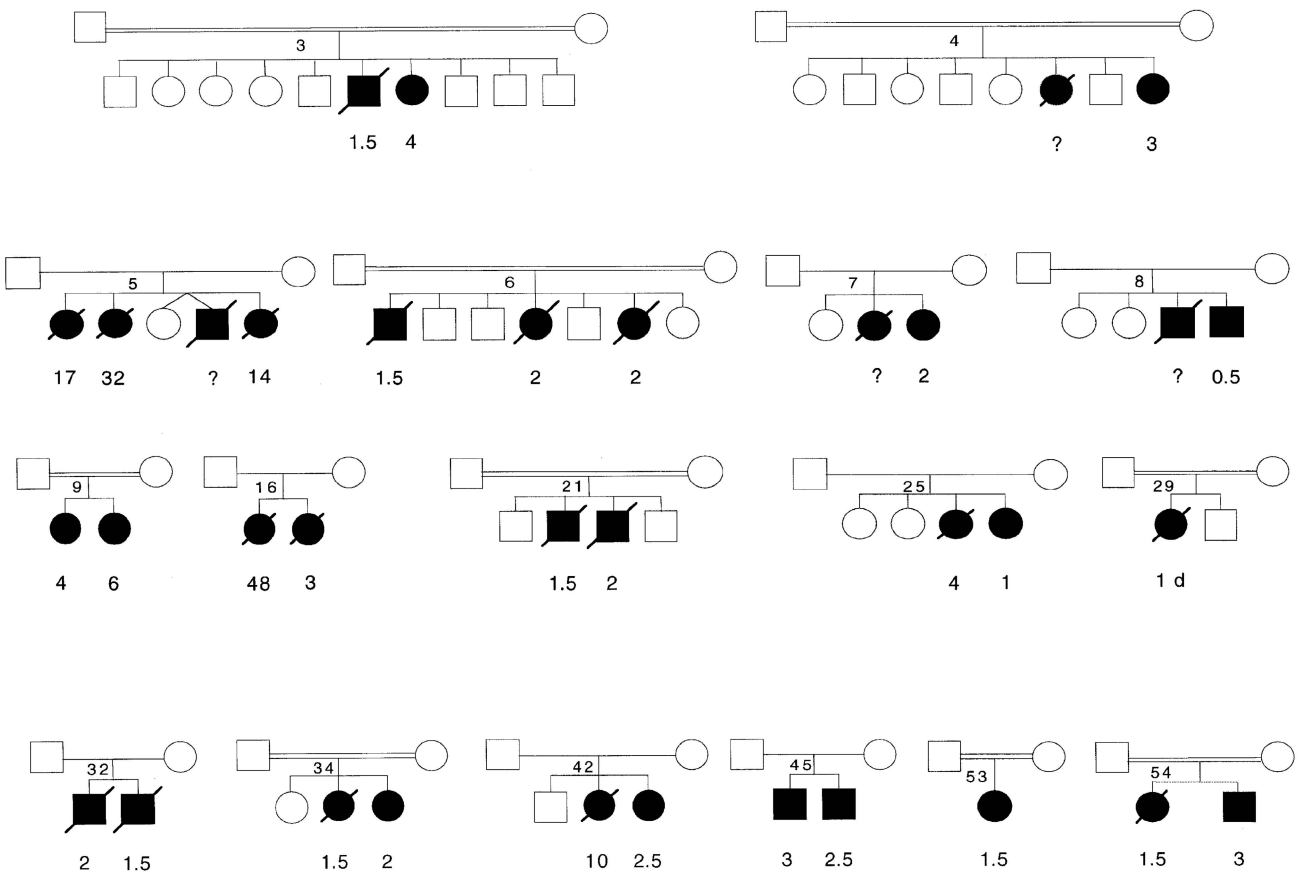

Figure 1 Pedigree of the 17 investigated FHL families. Age at disease onset, expressed in months, is indicated under the symbols for affected individuals.

verity of the hemophagocytic syndrome, the occurrence of relapse, evidence for autosomal recessive inheritance, and the absence of associated albinism. On the basis of these diagnostic features, we performed a whole-genome linkage analysis in 17 multiplex and/or consanguineous families with FHL, to map the FHL locus. We identified a locus (FHL1) on chromosome 10q21-22 as well as evidence for genetic heterogeneity of this condition.

Subjects and Methods

Patients and Families

Seventeen families referred either by the pediatric immunology and hematology unit at Hôpital Necker–Enfants Malades (11 families) or by other clinical units in France, the Netherlands, Germany, and Australia were investigated. FHL was diagnosed on the basis of clinical, immunological, biological, and genetic criteria, as discussed by Henter et al. (1998). Only families with either recurrence of the disease or consanguinity were analyzed. Diagnostic features included fever, hepatosplenomegaly, edema, and neurological abnormalities, accompanied by pancytopenia, liver cytolysis, hypertriglyceridemia, hypofibrinogenemia with evidence of hemophagocytosis in bone marrow, liver, and cerebrospinal fluid, and the presence of activated ($HLADr^+$) T lymphocytes in peripheral blood. None of the patients presented with either giant granulations in the cytoplasm of hematopoietic cells or partial oculocutaneous albinism. Diagnosis of either Chédiak-Higashi syndrome or Griscelli syndrome was therefore excluded. In families with male patients only, diagnosis of XLP was excluded either by the absence of Epstein-Barr virus (EBV) genomic sequences in patients' cells, as assessed by DNA PCR amplification (in patients from family 32); absence of EBV-specific IgM antibody response in patients whose disease onset occurred at <6 mo of age (in patients from families 21 and 32); or inheritance of different maternal X chromosomes at the XLP locus (in the affected brothers in family 45). This analysis was performed with polymorphic markers DXS1001 and DXS8044, which flank the XLP locus within a 6-cM genetic region (Coffey et al. 1998).

Onset of the disease is shown in figure 1. Onset oc-

curred at age <6 mo in patients from 16 of the 17 families. Nine of the 17 families were consanguineous. These families were of various origins: France, Portugal, northern Africa, Australia, Mali, Germany, and Turkey. A total of 86 subjects were investigated, 25 of whom were affected.

Marker Analysis

After informed consent was obtained, blood samples were collected from family members. DNA was extracted from leukocytes by standard methods. Polymorphic microsatellite markers were analyzed by use of PCR and PAGE. Genotyping was performed either with fluorescence-based techniques using an automated 373A DNA sequencer with GENESCAN and GENOTYPER software (Perkin-Elmer/Applied Biosystems) (Reed et al. 1994) or by radiolabeling using primers from the Généthon collection (Dib et al. 1996).

Linkage Analysis

A genomewide linkage search for the FHL locus was undertaken in the 17 families. The FASTLINK 2.2 package was used for genetic linkage analysis (Schaffer et al. 1994), and the GENEHUNTER 1.1 program (Kruglyak et al. 1996) was used for multipoint linkage analysis. Inheritance of FHL was considered to be autososomal recessive, with an estimated frequency of 0.006 and complete penetrance. Equal allele frequencies were used. Marker-allele frequencies were assumed to be equal. Heterogeneity tests were performed with the HOMOG program (Ott 1983).

Results

Linkage Analysis

In view of the dysregulated T-cell and macrophage–activation phenotype displayed by the FHL patients, we first genotyped the families by using intragenic or linked markers from regions containing candidate genes known to be involved in the regulation of T-cell and macrophage activation. We obtained no significant linkage in the families with the intragenic markers for the CTLA-4 (Polymeropoulos et al. 1991) and interleukin 10 (Eskdale and Gallagher 1995) genes or for the 3q13.3-q21,

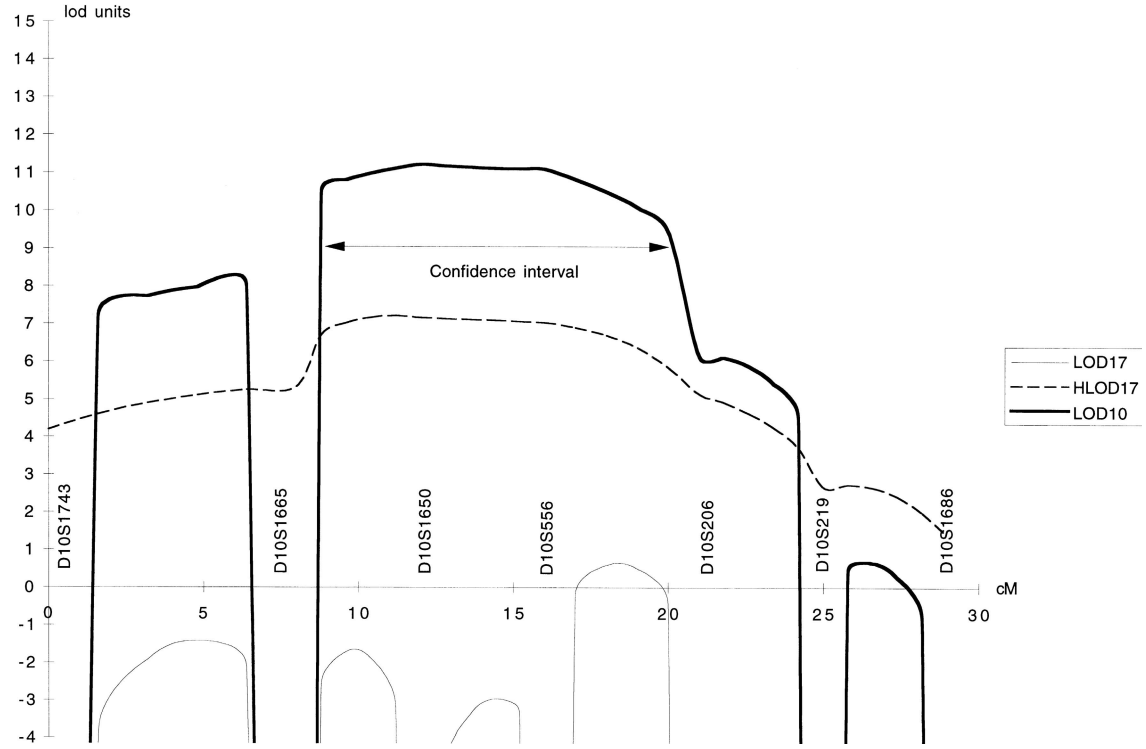

Figure 2 Results of multipoint LOD score analysis using GENEHUNTER. LOD17 was obtained under the hypothesis of homogeneity, when all the FHL families were considered. LOD10 was obtained when only the 10 FHL families linked to chromosome 10 were considered. HLOD17 shows the results of the LOD score analysis under the heterogeneity hypothesis, when all families were considered. The *X*-axis is the genetic distance (in centimorgans) and the *Y*-axis is LOD score units. The positions of the genetic markers used in multipoint analysis are drawn to scale on the *X*-axis. The centromere is located to the left of the graph and is not shown.

21q22.1, and 11q23.3 regions, containing CD80/CD86, the interleukin 10 receptor β chain, and the interleukin 10 receptor α chain genes, respectively (Selvakumar et al. 1992). We then randomly screened the genome by using 280 markers. We detected linkage between FHL1 and D10S201 on the long arm of human chromosome 10, with a maximum LOD score of 2.04 at maximum recombination fraction (θ_{max})=.057, under the hypothesis of homogeneity. Additional markers were used to confirm linkage to this region (table 1). A maximum LOD score of 2.85 (Z_{max}) was obtained for marker D10S1665, at θ=.13.

Table 1

LOD Scores between FHL1 Locus and Chromosome 10q21-22 Markers

	All 17 Families		10 Linked Families		7 Recombinant Families	
Marker	θ_{max}	Z_{max}	θ_{max}	Z_{max}	Z/θ = .001	θ/Z = −2.00
D10S1743	.18	1.27	.05	3.30	−16.45	.11
D10S1665	.13	2.85	.02	5.69	−15.25	.10
D10S1650	.13	2.31	.00	6.99	−14.44	.13
D10S556	.16	1.44	.00	5.40	−15.19	.12
D10S206	.09	2.14	.00	3.24	−3.31	.01
D10S219	.24	.81	.11	1.73	−14.96	.09
D10S1686	.18	1.04	.17	1.12	−15.25	.06

Evidence for Genetic Heterogeneity

Results of the two-point LOD score analysis are shown in table 1. Initial LOD-score analysis of each individual pedigree indicated that, in 7 of the 17 families studied, FHL disease occurrence did not map to chromosome 10q21-22 (families 3, 8, 9, 16, 32, 45, and 54) (not shown). The results from the other 10 families provided strong evidence for linkage with the markers in this region (table 1). No recombination was detected with D10S1650 (LOD score 6.99), D10S556 (LOD score 5.40), and D10S206 (LOD score 3.24). The heterogeneity hypothesis was therefore tested by use of the HOMOG program. As shown in table 2, for both tightly linked markers D10S1650 (α=.5; P=.012) and D10S556 (α=.5; P=.039), there was evidence of heterogeneity, indicating that, in approximately half of the FHL families, there was a linkage to the FHL1 locus.

Formal multipoint analysis was performed by use of the GENEHUNTER program and an overlapping set of seven markers at a time. The LOD score (LOD17) was negative over much of the region and reached a maximum of 0.58 distal to D10S556, under the hypothesis of genetic homogeneity (fig. 2). In contrast, if a heterogeneity hypothesis was assumed, a maximum LOD score (HLOD17) of 7.22 was attained at 0.8 cM proximal to D10S1650. Multipoint analysis restricted to the set of 10 families in which FHL is associated with chromosome 10 showed FHL1 linkage to the D10S1650 marker, with a maximum LOD score (LOD10) of 11.22.

In the seven other families, construction of haplotypes in each family confirmed the presence of multiple recombination events within the region defined by the tested markers. In the three consanguineous families, affected individuals inherited different chromosomes from their parents (as shown, for family 3, in fig. 3). In the four other families, both affected individuals inherited different haplotypes, or, conversely, both affected and normal sibs inherited identical haplotypes from both parents. Neither clinical nor pathological features of the

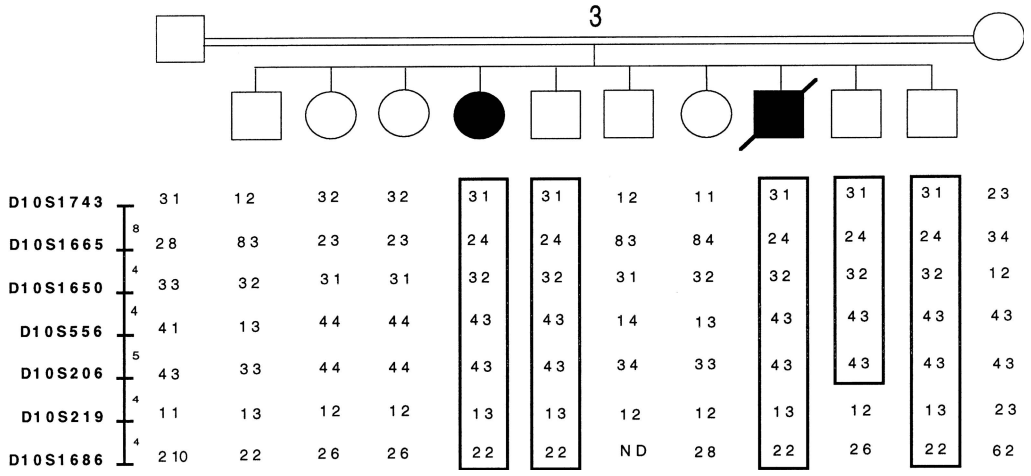

Figure 3 Pedigree of family 3 and haplotype analysis of markers of the 10q21-22 region, showing absence of linkage, in this FHL family, to this region of chromosome 10.

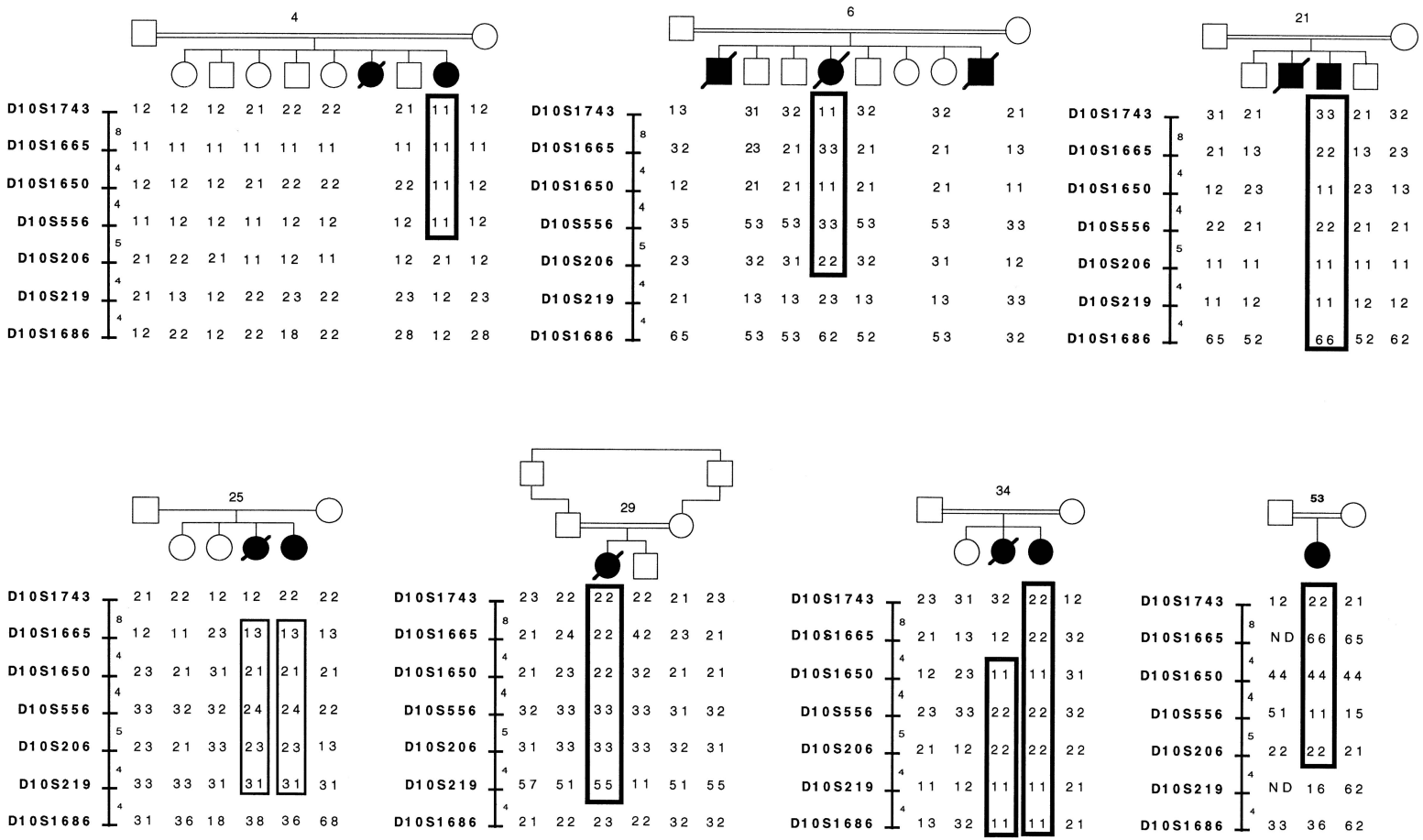

Figure 4 Genotypes of contributing families for determination of the critical interval. Thicker-outlined boxes indicate haplotypes homozygous by descent in consanguineous families; thinner-outlined boxes indicate haplotypes shared by descent in the nonconsanguineous family.

Table 2

Heterogeneity Analysis: HOMOG Analysis Results

Marker	α	χ^2	P
D10S1743	.35	1.458	.114
D10S1665	.5	2.103	.074
D10S1650	.5	5.110	.012
D10S556	.5	3.087	.039
D10S556	.6	.855	.178
D10S219	1	0	.5
D10S1686	1	0	.5

disease, however, differed between the subgroups of patients.

Haplotype Analysis of the Families with Linkage to FHL1

The genetic interval was defined in the remaining 10 families by haplotype analysis. Figure 4 depicts the haplotype segregation in seven of the pedigrees, including the six consanguineous families. Recombination events observed in affected individuals in families 4, 6, 25, 29, and 34 define a critical region between markers D10S206, telomerically, and D10S1665, centromerically. Thus, the FLH1 locus maps to the 13-cM interval between these markers.

Discussion

FHL is one of the HLH syndromes, a heterogeneous group of diseases characterized by hyperactivation of T cells and macrophages (Farquhar et al. 1952; Arico et al. 1996; Henter et al. 1998). FHL is one of four clearly inherited entities in this group. It can be distinguished from the other conditions that share autosomal recessive inheritance—that is, Chédiak-Higashi syndrome and Griscelli disease—since both of them cause partial albinism, as well as from XLP, by genetic segregation analysis and testing for the occurrence of EBV infection. These criteria were used to demonstrate that the families studied were not affected by these other inherited conditions. FHL should also be distinguished from the acquired HLH, often associated with viral infection, that occurs as sporadic cases, usually later in childhood. To avoid possible misdiagnosis of acquired forms, we restricted linkage analysis in our study to consanguineous and/or multiplex families with early onset of the disease.

Our data clearly establish the existence of a locus for FHL, on the proximal long arm of chromosome 10 (FHL1), in a 13-cM candidate region between markers D10S206 and D10S1665. Assignment of the FHL1 locus to this region places it with a group of four disorders previously mapped to the 10q21-22 region. These disorders include autosomal recessive deafness 12 (MIM 601386), cardiomyopathy dilated 1C (MIM 601493), congenital hypomyelinating neuropathy 1 (MIM 129010), and hemolytic anemia due to hexokinase deficiency (MIM 142600). Several partial and complete transcripts have been mapped to this region of chromosome 10. These include ankyrin 3 (MIM 600465), the β isoform of the catalytic subunit of the protein phosphatase 3 (MIM 114106), annexin VII (MIM 186360), the calcium/calmodulin-dependent protein kinase gamma (MIM 602123), and pore-forming protein (MIM 170280). If, as hypothesized, FHL gene function is involved in the negative regulation of T-cell activation, none of these genes represent candidates for FHL. Detailed screening of the partial transcript sequences (National Center for Biotechnology Information's Genemap 98) that map to the critical region is being performed to identify one of the genes involved in FHL.

This study shows that in only half the families is disease inheritance associated with the FHL1 locus, indicating that FHL is a genetically heterogeneous disease. Two-point and multipoint linkage analyses, HOMOG-test analysis, and haplotype inspection of each individual pedigree all showed evidence for heterogeneity, indicating the existence of at least a second locus for FHL. Genetic heterogeneity is a feature of a number of inherited disorders (Jarman et al. 1997; Weiler et al. 1998). However, because it is difficult to demonstrate significant linkage when a disease phenotype is associated with several loci, genetic heterogeneity is usually only described once a first locus has been identified—sometimes in a single family. The severity of FHL and its relatively low incidence required the study of a large panel of families of various origins, to increase the likelihood, during a first linkage study, of detection of genetic heterogeneity.

In some disorders, genetic heterogeneity can be correlated with either phenotypic divergence or different ethnic origins. In the case of FHL, the clinical and biological characteristics of the families in which the disease was linked to FHL1 were carefully compared with those of the other families. None of the criteria, including ethnic origin, age at onset, clinical presentation, biological features, or severity of the disease, enabled us to differentiate these two groups of patients. However, it is possible that there are more subtle differences, such as different cytokine-production profiles or lymphocyte-activation patterns. Study of additional families will be required, to refine the localization of the FHL1 locus. However, the absence of phenotypic criteria delineating the two groups of families with FHL makes it difficult to include those families in which only a short region encompassing the FHL1 locus segregates with FHL. Linkage studies are in progress in the families without linkage to the FHL1 locus, to identify the putative second locus for FHL. Ultimately, defining the genetic basis of this condition should lead to both improvement in

diagnosis and a better understanding of the pathogenesis of HLH disorders.

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Electronic-Database Information

National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/genemap98 (for Genemap 98)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for autosomal recessive FHL [MIM 267700]; Chédiak-Higashi syndrome [MIM 214500]; Griscelli syndrome [MIM 214450]; X-linked lymphoproliferative syndrome [MIM 308240]; autosomal recessive deafness 12 [MIM 601386]; cardiomyopathy dilated 1C [MIM 601493]; congenital hypomyelinating neuropathy 1 [MIM 129010]; hemolytic anemia due to hexokinase deficiency [MIM 142600]; and transcripts for ankyrin 3 [MIM 600465], the β isoform of the catalytic subunit of protein phosphatase 3 [MIM 114106], annexin VII [MIM 186360], kinase gamma [MIM 602123], and pore-forming protein [MIM 170280], which have been mapped to this region of chromosome 10)

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