*Am. J. Hum. Genet. 66:1693–1698, 2000*

# Report

## Identification of a Locus on Chromosome 1q44 for Familial Cold Urticaria

Hal M. Hoffman,[1] Fred A. Wright,[3] David H. Broide,[1] Alan A. Wanderer,[4] and Richard D. Kolodner[2]

[1]Department of Medicine and [2]Ludwig Institute of Cancer Research, Department of Medicine, and Cancer Center, University of California at San Diego; [3]Division of Human Cancer Genetics and Cancer Center, Ohio State University, Columbus; and [4]Department of Pediatrics and Allergy, University of Colorado Health Sciences Center, Denver

**Familial cold urticaria (FCU) is a rare autosomal dominant inflammatory disorder characterized by intermittent episodes of rash with fever, arthralgias, conjunctivitis, and leukocytosis. These symptoms develop after generalized exposure to cold. Some individuals with FCU also develop late-onset reactive renal amyloidosis, which is consistent with Muckle-Wells syndrome. By analyzing individuals with FCU from five families, we identified linkage to chromosome 1q44. Two-point linkage analysis revealed a maximum LOD score ($Z_{max}$) of 8.13 (recombination fraction 0) for marker D1S2836; multipoint linkage analysis identified a $Z_{max}$ of 10.92 in the same region; and haplotype analysis defined a 10.5-cM region between markers D1S423 and D1S2682. Muckle-Wells syndrome was recently linked to chromosome 1q44, which suggests that the two disorders may be linked to the same locus.**

Familial cold urticaria (FCU) was first described in 1940 by Kile and Rusk; it has also been referred to as familial polymorphous cold eruption (Martin et al. 1981), cold hypersensitivity (MIM 120100) (Shepard 1971), cold pathergy, and cold-specific vasomotor neuropathy (Urbach et al. 1941). Although the exact prevalence of FCU is unknown, ~20 different families whose members have FCU have been reported (Kile and Rusk 1940; Urbach et al. 1941; Witherspoon et al. 1948; Rodin and Bluefarb 1951; Tindall et al. 1969; Castelain 1971; Shepard 1971; Derbes and Coleman 1972; Doeglas 1973; Vlagopoulos et al. 1975; Commerford and Meyers 1977; Wanderer 1979; Martin et al. 1981; Roux et al. 1982; Fordyce and Coulson 1993; Ormerod et al. 1993; Zip et al. 1993; Kalogeromitros et al. 1995).

The clinical features of FCU include recurrent attacks of a nonpruritic, nonurticarial maculopapular exanthem associated with arthralgias, fever and chills, conjunctivitis, myalgias, headache, fatigue, and swelling of the extremities (Tindall et al. 1969; Zip et al. 1993). The onset of symptoms is delayed 30 min to 3 h after exposure to cold, and symptoms often persist 24–48 h. The most consistent laboratory finding is marked polymorphonuclear leukocytosis, which is found during attacks (Tindall et al. 1969; Doeglas and Bleumink 1974). The pathological changes in the skin of patients with FCU during attacks include a primarily polymorphonuclear leukocyte perivascular infiltrate, increased vascularity, and dermal edema, but no vasculitis (Martin et al. 1981; Tonnesen et al. 1985*a*; Zip et al. 1993). FCU manifests as early as birth but no later than early childhood, and it persists throughout the person's life. In general, people with FCU have normal longevity; however, patients with FCU from a subset of families studied (Shepard 1971) also have late-onset renal amyloidosis. Some of these patients were diagnosed with a variant of Muckle-Wells syndrome (MWS) (MIM 191900), a condition with variable expression that classically includes recurrent rash, late-onset progressive nerve deafness, and late-onset renal amyloidosis (Muckle 1979).

The only significant abnormalities of inflammatory mediators in FCU are elevations of granulocyte colony-stimulating factor, interleukin-6 (Urano et al. 1998), and acute-phase reactants such as C-reactive protein (Tonnesen et al. 1985*b*). Kinins, histamine, and other mast-cell mediator levels are normal (Tindall et al. 1969; Doeglas and Bleumink 1974). Neither cold agglutinins nor cryoglobulins are present (Vlagopoulos et al. 1975; Kalogeromitros et al. 1995). Despite numerous pathological

Received January 3, 2000; accepted for publication February 15, 2000; electronically published March 30, 2000.

Address for correspondence and reprints: Dr. Hal M. Hoffman, Division of Rheumatology, Allergy, and Immunology, University of California at San Diego, Mail Code 0635, 9500 Gilman Drive, La Jolla, CA 92093-0635. E-mail: hahoffman@ucsd.edu


0002-9297/2000/6605-0025$02.00

and biochemical investigations, the etiology of FCU remains unknown.

We studied five families that included a total of 69 individuals aged 1–80 years. Families 1, 2, and 3 were reported elsewhere (Shepard 1971; Vlagopoulos et al. 1975; Wanderer 1979). After informed consent was obtained with a protocol approved by the University of California at San Diego institutional review board, patients were evaluated to determine whether they were affected by FCU. Twenty-six of the 69 family members studied were affected. One 72-year-old affected individual from family 2 also had late-onset reactive renal amyloidosis, a condition reported in many of her affected ancestors but not in her monozygotic twin. (We determined monozygosity by genotyping >20 markers from three chromosomes.) Families 1 and 2 have extensive multigenerational pedigrees originating from northern Europe and dating back to the 18th century. These pedigrees are consistent with complete or near-complete penetrance, and no anticipation is apparent. In families 3, 4, and 5, the first affected family member was identified only in recent generations, which indicates possible de novo mutations, incomplete penetrance, or nonpaternity.

Genomic DNA was isolated from the whole blood of subjects by use of the PureGene DNA isolation kit (Gentra Systems). A whole-genome screening set was developed by means of sets available from the Cooperative Human Linkage Center, version 8.0, Marshfield Weber, version 8a, and Applied Biosystems Inc. (ABI Prism), version 2. Additional markers were identified with sex-averaged maps from the Cooperative Human Linkage Center, Center for Medical Genetics - Marshfield, WI, USA, ABI Prism, Whitehead Institute for Biomedical Research-MIT Center for Genome Research, Généthon, Genetic Location Database, and Genome Database. Fluorescently labeled PCR primers for all markers were synthesized by Gibco BRL (Life Technologies). PCR and automated genotyping were performed by standard ABI Prism protocols. Genotype scoring was performed in a blinded fashion with Fondation Jean Dausset - CEPH patients 1331 and 1332 as controls. Genotype and pedigree data were entered into Cyrillic 2.02 software (Cherwell Scientific).

Published marker allele frequencies from Fondation Jean Dausset - CEPH were used because all five FCU families were white and of northern European descent. Observed sample allele frequencies were used for two markers for which the Fondation Jean Dausset - CEPH allele frequencies were unavailable. Monozygotic twins from family 2 were treated as one individual with two marriages for the purpose of linkage analysis, which is appropriate because penetrance is near 1 (Terwilliger and Ott 1994). Two-point linkage analysis was performed by the MLINK program of the Linkage 5.2 package (Lathrop et al. 1984) with a dominance transmission model, a penetrance of 0.99, and a genetic frequency of 0.00001. Multipoint linkage analysis was conducted by the following sex-averaged map order: D1S3462 (18.3 cM)-D1S1594 (2.0 cM)-D1S304 (6.0 cM)-D1S404 (1.0 cM)-D1S1609 (3.3 cM)-D1S423 (4.0 cM)-AFMb005wh9 (4.0 cM)-D1S2836 (2.5 cM)-D1S2682. This analysis was performed by the GENEHUNTER program (Kruglyak et al. 1996) for families 2–5; the analysis could not be used for family 1 because of its large size. Because of limitations in the LINKAGE program, available from the Lab of Statistical Genetics, Rockefeller University, and in related programs (Terwilliger and Ott 1994), the program SIMPLE (Irwin et al. 1994) was used to perform a full multipoint linkage analysis of all nine markers on family 1. Linkage homogeneity was tested by the HOMOG program (Ott 1991) on both the two-point and multipoint results at the marker D1S2836.

A whole-genome screen was initiated with the use of data from family 1 only. After <5% of the screen was completed, a maximal two-point LOD score ($Z_{max}$) of 2.57 (recombination fraction [$\theta$] 0.06) was identified for D1S1609, the most telomeric marker on chromosome 1q from the screening set, prompting follow-up in that region. Maximal two-point LOD scores for the nearest markers in the screening set, D1S304 and D1S3462, were 0.99 ($\theta$ = 0.12) and 0.00 ($\theta$ = 0.47), respectively. We used a combination of databases to choose additional markers to saturate the region surrounding D1S1609 with an average resolution of 3 cM (range 1–6 cM). All five families were genotyped for all nine markers in the region, and LOD score data at incremental recombination fractions are shown (table 1). Maximal two-point LOD scores for five markers exceeded 3.00. The highest two-point LOD scores obtained were 8.13 ($\theta$ = 0.00) and 7.99 ($\theta$ = 0.03), for markers D1S2836 and D1S2682, respectively. Linkage analysis at all nine markers was performed on all families except family 3; we omitted family 3 because data from its members were uninformative for linkage, but it was included in the study for haplotype analysis. Multipoint linkage analysis of all nine markers for family 1 by SIMPLE resulted in a maximum multipoint LOD score of 7.19 distal to D1S423. Multipoint linkage analysis of families 2, 4, and 5 by GENEHUNTER achieved a LOD of 4.27 between D1S423 and D1S2682. The combined multipoint LOD for families 1, 2, 4, and 5 (fig. 1) achieved a $Z_{max}$ of 10.92 in the interval between D1S423 and D1S2682. A one-LOD support interval (Conneally et al. 1985) spans most of the D1S423–D1S2682 region. No evidence of genetic heterogeneity among the families was detected at marker D1S2836, with the maximum likelihood estimate of the linkage proportion at $\alpha$ = 1.

Haplotype analysis in all five families is shown in fig-

ure 2. Informative recombinant events were seen in the following family 1 members: affected patient 5 between D1S423 and D1S2836 (AFMb005wh9 was not informative); unaffected patient 24 between D1S1609 and D1S423; affected patient 28 between D1S3462 and D1S1594; and unaffected patient 29 between D1S1594 and D1S304. The parents of affected patient 8 were not available for study, but he shared a haplotype consisting of the five most telomeric markers with his distant relatives. Informative recombinant events were seen in two family 2 members: affected patient 34 between D1S1609 and AFMb005wh9 (D1S423 was not informative), and affected patient 41 between D1S2836 and D1S2682. Recombination events in family 4 occurred in affected patient 46 and unaffected patient 50 between D1S3462 and D1S1594. There were no informative recombination events in families 3 and 5 and no strong evidence for a shared haplotype between families 1 and 2. Recombinational analysis of all family data defined a centromeric limit at D1S423 and a telomeric limit at D1S2682, a region of ~10.5 cM.

This is the first comprehensive report of clear genetic linkage for FCU in several families. Our data are in agreement with data presented in abstract form (Jung et al. 1996) that showed linkage to 1q44 with a $Z_{max}$ of 7.83 at D1S2836 in two FCU families. Jung et al. defined a larger region between D1S102 and the telomere. We delineate a narrower region bound by a centromeric polymorphic marker (D1S423) that is considerably distal to D1S102 and a telomeric polymorphic marker (D1S2682) that is considerably proximal to the telomere.

The linkage of both FCU and MWS to 1q44 and the presence of patients with both distinct phenotypes provides additional information regarding the genetic linkage of the FCU phenotype. Both conditions are characterized by recurrent episodes of rash, arthralgia, myalgia, fever, conjunctivitis, and leukocytosis and by elevated serum interleukin-6 levels (Gerbig et al. 1998; Urano et al. 1998). However, patients with FCU develop these symptoms only after exposure to cold, and patients with MWS develop symptoms without such exposure. Patients with MWS variably express late-onset nerve deafness and renal amyloidosis (Muckle 1979; Gerbig et al. 1998), but these phenotypes are not seen in families with FCU alone. Therefore, there is a distinct constellation of symptoms common to both syndromes, but the correlation to cold exposure is unique to FCU and the nerve deafness is unique to MWS. MWS has been linked to chromosome 1q44 in three families with a $Z_{max}$ of 4.66 at D1S2836 and a region defined by recombinational analysis of 13.9 cM between D1S2811 and D1S2682 (Cuisset et al. 1999).

The phenotype similarity and genetic linkage to the same region could be explained in several ways. Microdeletions of different sizes in the region of two close but

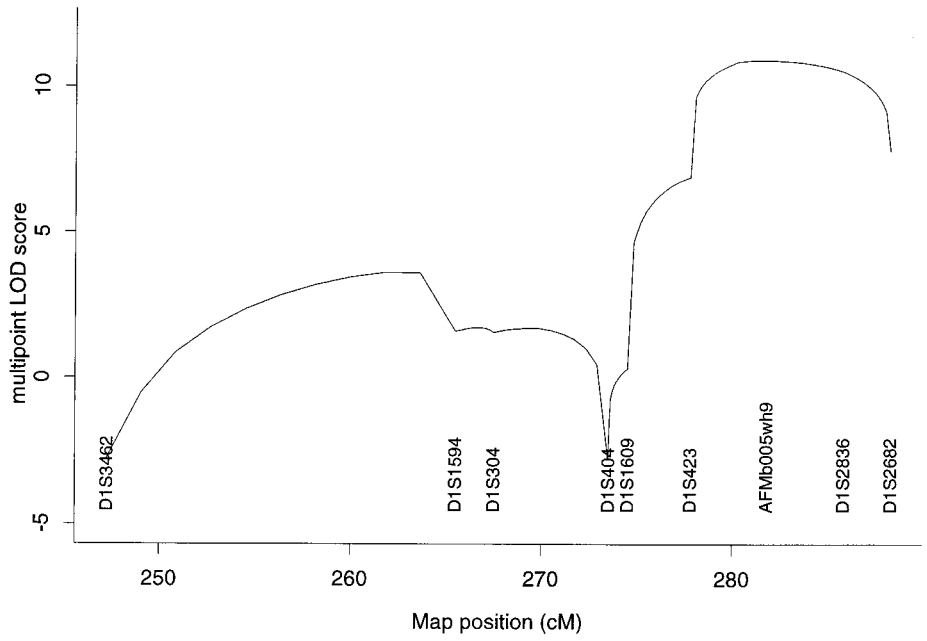


**Figure 1** Multipoint linkage analysis between FCU and nine markers on chromosome 1q43-q44. Genotype information from individuals from four families was used. Genetic distances between markers are expressed in centimorgans and are calculated on the basis of the sex-averaged map of the Center for Medical Genetics - Marshfield, WI, USA. Multipoint analysis for family 1 was performed separately, because of its large size; family 1 data were combined with data from families 2, 4, and 5.

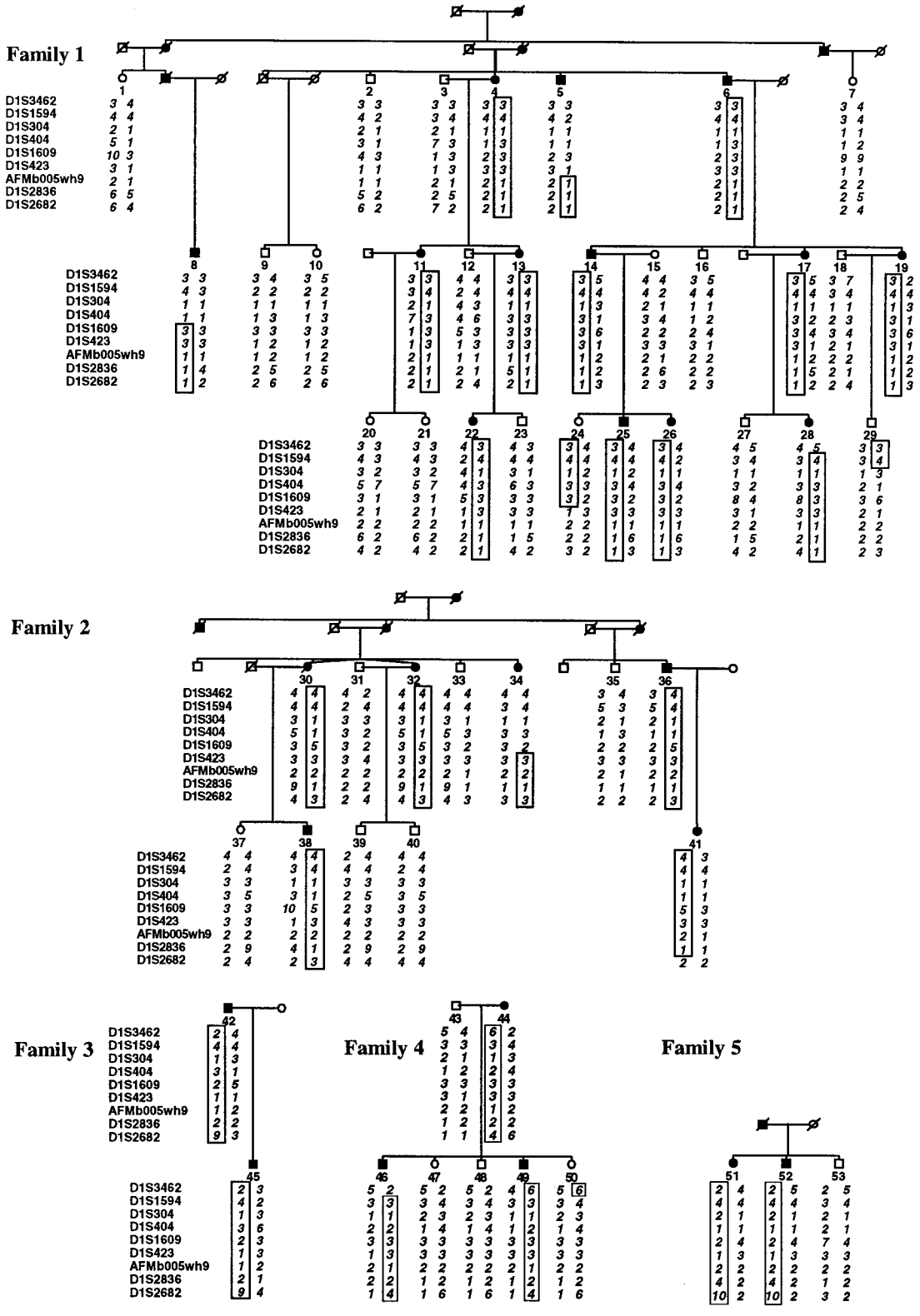


**Figure 2** Haplotypes for nine markers from 1q43-q44 for five families with FCU. Genetically uninformative cases are not included. Marker order is shown to the left of each generation. Disease-linked haplotypes are indicated by being boxed. Key recombination events are observed between D1S423 and D1S2836 in patient 5 (family 1), between D1S1609 and D1S423 in patient 34 (family 2), and between D1S2836 and D1S2682 in patient 41 (family 2).

**Table 1**

**Cumulative Two-Point Linkage Analysis for Individuals with FCU from Four Families**

| | LOD Score at $\theta$ = | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Marker | .00 | .01 | .05 | .1 | .2 | .3 | .4 | $Z_{max}$ | $\theta$ |
| D1S3462 | −20.43 | −6.54 | −3.66 | −2.28 | −.97 | −.36 | −.06 | .00 | .48 |
| D1S1594 | 1.66 | 1.63 | 1.52 | 1.37 | 1.04 | .65 | .24 | 1.66 | .00 |
| D1S304 | 2.46 | 2.69 | 2.89 | 2.79 | 2.24 | 1.49 | .66 | 2.89 | .05 |
| D1S404 | −10.16 | .34 | 2.44 | 2.95 | 2.69 | 1.77 | .72 | 2.98 | .12 |
| D1S1609 | −2.84 | 3.45 | 4.15 | 4.10 | 3.39 | 2.37 | 1.20 | 4.18 | .07 |
| D1S423 | 4.01 | 3.94 | 3.63 | 3.24 | 2.44 | 1.60 | .75 | 4.01 | .00 |
| AFMb005wh9 | 5.37 | 5.27 | 4.83 | 4.27 | 3.09 | 1.85 | .70 | 5.37 | .00 |
| D1S2836 | 8.13 | 7.99 | 7.42 | 6.69 | 5.14 | 3.44 | 1.62 | 8.13 | .00 |
| D1S2682 | 3.70 | 7.86 | 7.85 | 7.23 | 5.57 | 3.62 | 1.57 | 7.99 | .03 |

separate genes could result in individuals with one or both phenotypes. The phenotypic pattern observed could also be explained by two genes that code for products in the same pathway or by variable mutations in a common promoter for both genes. It is also possible that FCU and MWS represent different mutations within a single gene or variable expression of the same gene because of genetic or environmental factors.

Recently, the molecular and genetic bases of several autoinflammatory or periodic fever disorders have been elucidated, including familial Mediterranean fever, familial Hibernian fever, and familial periodic fever (Grateau et al. 1999). As with FCU, these disorders present as self-limited episodes of fever with synovial and cutaneous inflammation. However, unlike FCU, serosal inflammation such as sterile peritonitis and pleurisy are common features of these conditions. As with MWS, the primary morbidity in these disorders is from renal amyloidosis. FCU and MWS may be seen as members of this group of disorders. As further studies are conducted, the molecular basis of these inflammatory disorders may shed light on the mechanisms involved in FCU and MWS.

Sensitivity to cold is the one unique feature of FCU and is perhaps the most intriguing mechanism to unravel. The identification of the gene underlying FCU will not only be of importance in understanding the pathophysiology and possible treatment of FCU, but may also provide insight into mechanisms of other chronic inflammatory processes and the inflammatory responses induced by physical stimuli such as cold.

## Acknowledgments

We are extremely grateful to all the family members who participated in this research effort. We also thank John Weger and Jill Sansone, for technical assistance with genotyping; Xin Gao, for technical assistance with linkage analysis; Mark Tresierras and Daniel Lightfoot, for general laboratory assistance; James Schmeits, for his expertise in robotics and informatics; Michael Kane, for practical laboratory advice; and Ruchira Das Gupta, William Biggs, and Webster Cavenee, for helpful advice and guidance. The statistical analysis computers were supported by NIGMS GM58934. The research was performed with the support of the National Institutes of Health (NIAID 5-K08 AI01508), the American Academy of Allergy, Asthma, and Immunology Education and Research Trust Faculty Development Award, and the Ludwig Institute of Cancer Research.

## Electronic-Database Information

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

ABI Prism, http://www.pebio.com/ga/linkagemaps/ (for microsatellite marker information)
Center for Medical Genetics - Marshfield, WI, USA, http://www.marshmed.org/genetics/ (for microsatellite marker information)
Cooperative Human Linkage Center, http://lpg.nci.nih.gov/CHLC (for microsatellite marker information)
Fondation Jean Dausset - CEPH, http://www.cephb.fr/ (for CEPH genotype information)
Généthon, http://www.genethon.fr (for microsatellite marker information)
Genetic Location Database, http://cedar.genetics.soton.ac.uk/ (for microsatellite marker information)
Genome Database, http://www.gdb.org/ (for microsatellite marker information)
Lab of Statistical Genetics, Rockefeller University, ftp://linkage.rockefeller.edu/software/ (for LINKAGE software)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for cold hypersensitivity [MIM 120100] and for MWS [MIM 191900])
Whitehead Institute for Biomedical Research-MIT Center for Genome Research, http://www-genome.wi.mit.edu (for microsatellite marker information and for GENEHUNTER software)

## References

Castelain PY (1971) Urticaire familiale au froid. Bull Soc Fr Dermatol Syphiligr 78:525–526
Commerford PJ, Meyers OL (1977) Arthropathy associated with familial cold urticaria. S Afr Med J 51:105–108
Conneally PM, Edwards JH, Kidd KK, Lalouel JM, Morton

NE, Ott J, White R (1985) Report of the Committee on Methods of Linkage Analysis and Reporting. Cytogenet Cell Genet 40:356–359

Cuisset L, Drenth JP, Berthelot JM, Meyrier A, Vaudour G, Watts RA, Scott DG, et al (1999) Genetic linkage of the Muckle-Wells syndrome to chromosome 1q44. Am J Hum Genet 65:1054–1059

Derbes VJ, Coleman WP (1972) Familial cold urticaria. Ann Allergy 30:335–341

Doeglas HM (1973) Familial cold urticaria. Arch Dermatol 107:136–137

Doeglas HM, Bleumink E (1974) Familial cold urticaria. Clinical findings. Arch Dermatol 110:382–388

Fordyce AM, Coulson IH (1993) Familial cold urticaria—a rare cause of lip swelling. Br Dent J 175:417–418

Gerbig AW, Dahinden CA, Mullis P, Hunziker T (1998) Circadian elevation of IL-6 levels in Muckle-Wells syndrome: a disorder of the neuro-immune axis? QJM 91:489–492

Grateau G, Drenth JP, Delpech M (1999) Hereditary fevers. Curr Opin Rheumatol 11:75–78

Irwin M, Cox N, Kong A (1994) Sequential imputation for multilocus linkage analysis. Proc Natl Acad Sci USA 91: 11684–11688

Jung M, Ross B, Wienker TF, Preuss G, Kuester W, Ries A (1996) A locus for familial cold urticaria maps to distal chromosome 1q: familial cold urticaria and Muckle-Wells-syndrome are probably allelic. Am J Hum Genet Suppl 59: A223

Kalogeromitros D, Katsarou A, Armenaka M, Polizou E, Zografakis I, Stratigos I (1995) Familial cold urticaria: a father and daughter with typical clinical and laboratory features. Ann Allergy Asthma Immunol 74:295–298

Kile RL, Rusk HA (1940) A case of cold urticaria with an unusual family history. JAMA 114:1067–1068

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58:1347–1363

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

Martin S, Eastern J, Knox JM (1981) Familial polymorphous cold eruption. Cutis 27:173–175

Muckle TJ (1979) The "Muckle-Wells" syndrome. Br J Dermatol 100:87–92

Ormerod AD, Smart L, Reid TM, Milford-Ward A (1993) Familial cold urticaria. Investigation of a family and response to stanozolol. Arch Dermatol 129:343–346

Ott J (1991) Analysis of human genetic linkage. Johns Hopkins University Press, Baltimore

Rodin HH, Bluefarb SM (1951) Cold urticaria. J Indiana Med Assoc 44:846–847

Roux H, Gaborit P, Chabrier P, Sayag J, Weiller M (1982) Familial cold urticaria: apropos of a case [in French]. Rev Rhum Mal Osteoartic 49:131–135

Shepard MK (1971) LLL-cold hypersensitivity. In: Bergsma D (ed) The Third Conference on the Clinical Delineation of Birth Defects, part 12: skin, hair, and nails, vol 7, Williams and Wilkins, Baltimore, p 352

Terwilliger JD, Ott J (1994) Handbook of human genetic linkage. Johns Hopkins Press, Baltimore

Tindall JP, Beeker SK, Rosse WF (1969) Familial cold urticaria: a generalized reaction involving leukocytosis. Arch Intern Med 124:129–134

Tonnesen MG, Clark RAF, Siegal SL, Reed BR, Capin L, Wanderer AA (1985*a*) Cyclic endothelial cell injury and chronic blood vessel wall alterations in familial cold urticaria. Clin Res 33:690

Tonnesen MG, Giclas PC, Clark RAF, Wanderer AA (1985*b*) Immunopathology of familial cold urticaria. Paper presented at Aspen Allergy Conference, Aspen, July 26–29

Urano Y, Shikiji T, Sasaki S, Fukuhara K, Arase S (1998) An unusual reaction to cold: a sporadic case of familial polymorphous cold eruption? Br J Dermatol 139:504–507

Urbach E, Herrman MF, Gottlieb PM (1941) Cold allergy and cold pathergy. Arch Dermatol Syphilol 43:366–374

Vlagopoulos T, Townley R, Villacorte G (1975) Familial cold urticaria. Ann Allergy 34:366–369

Wanderer AA (1979) An "allergy" to cold. Hosp Pract 14: 136–137

Witherspoon FG, White CB, Hailey H (1948) Familial urticaria due to cold. Arch Dermatol Syphilol 58:52–55

Zip CM, Ross JB, Greaves MW, Scriver CR, Mitchell JJ, Zoar S (1993) Familial cold urticaria. Clin Exp Dermatol 18: 338–341