Background: Acquired cold urticaria (ACU) is usually a self-limited, sporadic, cutaneous disease diagnosed based on history and a positive cold stimulation time test (CSTT) result. We describe 3 unrelated families (A, B, and C) with lifelong atypical cold urticaria distinguished from ACU and familial cold autoinflammatory syndrome.

Objective: We sought to describe a new hereditary disease of cold urticaria and study its pathogenesis.

Methods: Questionnaires, interviews, physical examinations, skin testing, and biopsies were performed. Absolute values, means, and prevalence percentages of data are reported.

Results: Thirty-five subjects are described with familial atypical cold urticaria (FACU; family A, 17; family B, 8; and family C, 10) displaying an autosomal dominant pattern of inheritance. All tested subjects had negative CSTT results. Completed questionnaires from affected and unaffected members of families A and B (n = 35) revealed that all affected subjects had lifelong symptoms that began in early childhood with pruritus, erythema, and urticaria after cold exposure. Angioedema (family A, 23%; family B, 42%) and syncope, near syncope, or both (family A, 46%; family B, 86%) were also present.

Triggers included cold atmosphere (100%), aquatic activities (family A, 92%; family B, 100%), handling cold objects (family A, 54%; family B, 71%), and ingestion of cold foods or beverages (family A, 69%; family B, 100%). Skin biopsy specimens demonstrated a mast cell infiltrate with the appearance of degranulation after cold challenge.

Conclusions: FACU is a new cold-induced inherited disease that is different than ACU in its natural history, atmospheric cold elicitation, severity of systemic reactions, and CSTT results. FACU differs from familial cold autoinflammatory syndrome in symptom timing and the absence of fever, chills, and joint pain. The cause is suspected to be mast cell related. Treatment of reactions is similar to that for ACU. Further evaluation of pathogenesis and genetics is warranted. (J Allergy Clin Immunol 2009;124:1245-50.)

Key words: Cold urticaria, autosomal dominant, pedigree, questionnaire, cold stimulation time test, evaporative cooling, skin biopsy, mast cell, antihistamine, epinephrine

Cold urticaria is one of the physical urticarias in which patients experience pruritic urticaria, angioedema, or both from direct contact with cold, ingestion of cold foods or beverages, handling cold objects, and, to a lesser degree, exposure to ambient cold. Patients are at risk for anaphylaxis and cardiovascular collapse, especially when involved with aquatic activities.

Cold urticaria is diagnosed based on a suggestive history, physical examination, and positive cold stimulation time test result. A CSTT result is positive if cutaneous cold contact, usually with ice, produces a wheal-and-flare reaction at the time and site of the cold stimulation. Cold urticaria can be divided into acquired forms, including acquired cold urticaria (ACU) with a positive CSTT result, atypical ACU with a negative CSTT result, and 2 familial forms, including delayed cold urticaria and familial cold autoinflammatory syndrome (FCAS).

ACU is thought to be sporadic and is classified as either primary (usually idiopathic) or secondary (caused by cryoglobulinemia, an infectious disease, or leukocytoclastic vasculitis).

ACU usually affects young adults, with a mean duration of disease of 4 to 5 years and remission or improvement in symptoms in the majority of the patients within 5 years. Atypical ACU has been subdivided into delayed cold urticaria, cold-dependent cholinergic urticaria, cold-dependent dermatographism, and systemic cold urticaria.

Patients with cold-induced cholinergic urticaria experience generalized punctate urticaria after exercising in cold environments, whereas patients with cold-dependent dermatographism urticate after stroking precooled skin. Patients with systemic cold urticaria usually have severe urticarial symptoms with a tendency toward generalized systemic reactions after exposure to unique cold conditions.

Familial delayed cold urticaria is an autosomal dominant disease characterized by pruritic urticarial-like lesions that develop 9 to 18 hours after cold stimulation and can resolve into hyperpigmented macules.

CSTT results are immediately negative, but urtication occurs several hours later at the site of testing. FCAS is an autosomal dominant disease included in the family of inherited systemic autoinflammatory diseases. With generalized cold exposure, patients experience fever, joint, and eye symptoms along with an atypical, nonpruritic urticarial rash. In affected skin a neutrophilic infiltration is observed without evidence of mast cell degranulation.

We describe a new familial form of cold urticaria, familial atypical cold urticaria (FACU), in 3 unrelated multigenerational
families. Affected patient presentations do not conform to any one of the atypical ACUs and have distinguishing characteristics from both ACU and FCAS. Similar to ACU, the pathophysiology of FACU is undetermined, but our results suggest it to be mast cell mediated. FACU is a new hereditary cold urticaria and should be considered in patients with a suggestive personal and family history and a negative CSTT result.

METHODS
Clinical assessment

After informed consent was obtained, subjects were evaluated for clinical characteristics associated with atypical cold urticaria by using a protocol approved by the University of California–San Diego Human Research Protection Program. A total of 35 patients (20 affected and 15 unaffected) from families A (13 affected and 9 unaffected) and B (7 affected and 6 unaffected) participated. Two affected members of family C were clinically assessed, but none participated in the questionnaire. Interviews for families A and B were performed in person, by telephone, and by e-mail. Physical examinations were performed on subjects when possible. All 35 participating patients (or guardians) completed a 36-point written questionnaire to characterize their clinical features. Written answers were compiled and averaged when appropriate.

Allergy skin prick tests were performed with allergen extract for geographic common aeroallergens. Varied durations of CSTTs were performed with cold contact (ice covered by plastic) over a 5 × 3-cm² area of skin for 3 (6 children), 5 (5 adults), or 10 (2 adults) minutes followed by a 5-minute rewarming period at room temperature. The presence of erythema, wheal, or both was recorded. Five adult patients were subsequently immediately tested for cold-induced dermatographism at the site of cold stimulation. Evaporative cooling tests were performed with room temperature tap water placed on patient skin followed by air occlusion for 10 minutes and measurement of the reaction. A second drop was placed on the skin and exposed to compressed air, and the reaction was recorded. This process was repeated with 100% ethanol.

Punch biopsy specimens of dry unmoistened skin were performed in sterile fashion on 2 affected subjects from family B after exposure to room temperature for 3 hours. The right upper back was prepared and anesthetized with a 0.2-mL lidocaine HCl 1% and epinephrine 1:100,000 USP subcutaneous injection. One 4-mm punch biopsy specimen was taken from each subject followed by the placement of a single 4-0 nylon suture. The patients were then cold challenged for 15 minutes in a dry outdoor environment at temperatures of approximately 5°C with their upper backs exposed. A second biopsy was performed immediately over an erythematos site within 2 cm of the first biopsy in the same fashion. Normal control samples were obtained after a 30-minute cold challenge at 5°C.

FIG 1. Family Pedigrees: family A, B, C. Filled symbols represent affected individuals, open symbols represent unaffected individuals.

FIG 2. Cutaneous manifestations of 2 affected siblings from family B (A and B) and 1 affected child from family A (C). Fig 2, A, Sixteen-month-old boy after a 5-minute exposure to 5°C atmosphere outdoor exposure followed by 5 minutes at room temperature. Fig 2, B, Thirty-four-month-old boy at room temperature for 2 hours, crying. Fig 2, C, Four-year-old girl bathing indoors at room temperature.
Immunohistochemistry
Skin biopsy specimens were fixed in formalin, embedded in paraffin, sectioned, mounted on slides, deparaffinized, and rehydrated before analysis. Sections were subjected to staining with hematoxylin and eosin dyes. Tissue mast cell staining was done with primary mouse monoclonal IgG against tryptase (Abcam, Inc, Cambridge, Mass) at 1:150 dilution, secondary biotinylated antibody to mouse IgG at 1:200 dilution, peroxidase-labeled avidin detection (Vector ABC PK-6102; Vector Laboratories, Burlingame, Calif), and DAB chromagen (DAB Substrate Kit for Peroxidase SK-4100, Vector Laboratories). Hematoxylin was used for counterstaining. Slides were dehydrated and mounted with Cytoseal. Staining was also performed on 3 normal control skin biopsy samples.

Statistical analysis
Data were expressed as means and prevalence percentages of analyzed data.

RESULTS
Pedigree analysis
Three families, A, B, and C (Fig 1), are described with FACU, with a total of 35 affected subjects (age range, 6 months to 78 years). Each family noted 4 generations of affected individuals and traced the origin of the symptoms to 1 ancestor. The families are geographically dispersed (family A: Illinois, Texas, and California; family B: Colorado; family C: California and Guatemala), ethnically diverse (families A and B: White; family C: Hispanic), and not believed to be related to each other. All the families demonstrate an autosomal dominant pattern of inheritance. Male and female subjects are equally affected, and the vertical transmission rates of the disease for families A (17 affected subjects; 9 female subjects), B (8 affected subjects; 3 female subjects), and C (10 affected subjects; 4 female subjects) are 61%, 62%, and 45%, respectively.

Dermatologic features
FACU cutaneous reactions, which were observed in subjects from all 3 families, included pruritic erythema with urticaria, angioedema, or both after direct contact with a cold environment or object. The distribution of the rash appeared to be related to the area of cold exposure and in some circumstances (i.e., swimming) encompassed the entire body. However, localized cutaneous reactions did not generalize. Typical reactions are depicted in Fig 2. Skin exposed to ambient cold (5°C) for 5 minutes showed diffuse erythema and isolated wheal formation (above the right brow) of the exposed skin (Fig 2, A). A patient’s tear, at room temperature, produced erythema along the line of the teardrop (Fig 2, B) within 1 minute. Skin submerged in warm water did not react; however, when exposed to room temperature air (upper body, arm, and face), it became pruritic and erythematous (Fig 2, C). This is distinguished from aquagenic urticaria in which immersion into water, emersion from water, or both should produce urticaria.

Cutaneous testing
FACU-affected patients from all 3 families had negative CSTT results and experienced erythema without a wheal after 5 minutes.
of cold contact and 5 minutes of rewarming (Fig 3, A). Similar results were seen with 3 or 10 minutes of testing. Patients were followed for up to 2 hours after the CSTT. Erythema remained for an average of 30 minutes without the development of a wheal reaction, and no distant cutaneous reactions occurred from the site of testing (data not shown). One of the 5 adult patients had a positive cold-induced dermatographism test result. Patients who were outdoor cold challenged experienced erythema and isolated urticarial lesions over skin that was not protected by clothing, including their face, neck, upper back, chest, and arms. Their cutaneous reactions did not spread, and they did not experience any concomitant systemic symptoms. Reactions resolved within 30 minutes of rewarming at room temperature (data not shown).

Evaporative cooling tests were performed to further delineate the nature of the patients’ cutaneous reactions. Room temperature water was placed on the skin and covered for 10 minutes. This prevented evaporation and the development of erythema, urticaria, and pruritus (Fig 3, B). Exposing the droplet and surrounding skin to compressed air (Fig 3, C) produced erythema and limited urticaria at the site of the droplet. Results were similar with ethanol (image not shown).

A history of atopy (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, asthma, or food allergy) was reported in 84% of affected subjects in family A and 14% of affected subjects in family B. Allergy skin prick test responses of affected subjects were positive for only 1 of the 6 subjects tested in family B.

Questionnaire results

Age of onset within the first 6 months of life was reported in 77% and 100% of affected patients from families A and B, respectively. Mean age of presentation for families A and B was 3.75 years and 6 months, respectively (Table I), with a range of 6 months to 15 years. All subjects noted a lifelong duration of symptoms, and most noted a subjective improvement of the severity of their symptoms after 30 years of age.

Although all affected family members noted cutaneous pruritic erythema and urticaria after cold exposure, less than 50% of subjects experienced angioedema (Table I). Oropharyngeal swelling, abdominal pain, or both were triggered by the ingestion of cold foods or beverages in 29% and 43% of families A and B, respectively. Both groups also noted syncope or near syncope at varying degrees (Table I) that was usually related to their emergence from aquatic activities. Most patients developed their cutaneous symptoms within 5 minutes of cold exposure. The mean symptom duration was 35 minutes (Family A: 23 minutes; Family B: 46 minutes), with a range of 12 minutes to 24 hours depending on the continuation of cold exposure, institution of treatment, or both. Although no absolute atmospheric temperature was reported to elicit symptoms, humid and cool air was the most reproducible precipitant recorded.

The majority of patients noted that cutaneous drying and warming improved their symptoms within 30 to 60 minutes (Family A: 78%; Family B: 88%). Antihistamine use was minimal but reportedly provided complete relief and prophylaxis in 1 subject from family B who was treated with cyproheptadine 30 years ago. After discontinuation because of sedation, the patient’s symptoms returned. Multiple members of both families (Family A: 36%; Family B: 50%) used loratadine, cetirizine, or both at varying lengths and had a subjective reduction in their symptom severity, mainly pruritus, by 50%. Both families noted antihistamine prophylaxis to be superior to the treatment of cold contact and 5 minutes of rewarming (Fig 3, A). Similar results were seen with 3 or 10 minutes of testing. Patients were followed for up to 2 hours after the CSTT. Erythema remained for an average of 30 minutes without the development of a wheal reaction, and no distant cutaneous reactions occurred from the site of testing (data not shown). One of the 5 adult patients had a positive cold-induced dermatographism test result. Patients who were outdoor cold challenged experienced erythema and isolated urticarial lesions over skin that was not protected by clothing, including their face, neck, upper back, chest, and arms. Their cutaneous reactions did not spread, and they did not experience any concomitant systemic symptoms. Reactions resolved within 30 minutes of rewarming at room temperature (data not shown).

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Immunohistochemistry

Skin biopsy specimens were stained for mast cell tryptase. At room temperature, there appeared to be an increased presence of mast cells throughout the dermis and around the vasculature in our subjects (Fig 4, A) compared with that seen in normal control skin after cooling (Fig 4, C). After cold challenge, mast cells were present and appeared degranulated in the dermis and around the vasculature (Fig 4, B) compared with those seen in control samples after cooling (Fig 4, C).

### DISCUSSION

FACU is a newly described familial form of cold urticaria. Data from 2 families suggest the most consistent symptoms are early-onset, lifelong, localized pruritic erythema with urticaria, angioedema, or both after localized or atmospheric cold exposure in patients with a negative CSTT result. The presentation of FACU is limited to exposed skin without generalization and systemic reactions are not as severe. FACU symptoms occur immediately after cold exposure in contrast to delayed cold urticaria and its familial form.

| TABLE II. Distinguishing features of FACU, ACU, and FCAS |
|---------------------------------|-----------------|-----------------|
| Inheritance pattern | FACU | ACU | FCAS |
| Known genetic mutation | Unknown | Usually sporadic | Autosomal dominant |
| Onset in early childhood | +++ | – | +++ |
| Lifelong duration | +++ | – | +++ |
| Atmospheric cold elicitation | ++ | + | ++ |

**TABLE III. Proposed diagnostic criteria for FACU**

1. Rash: Localized pruritic erythema after cold exposure with urticaria, angioedema, or both
2. Autosomal dominant pattern of disease inheritance
3. Rash resolution usually <1 h after rewarming
4. Absence of fever, chills, or joint complaints
5. Age of onset in childhood with lifelong duration of symptoms
6. Negative CSTT result (no wheal formation)

The above diagnostic criteria are strongly suggestive of FACU and are helpful in distinguishing it from ACU and FCAS.

FACU, ACU, and FCAS do have overlapping characteristics with some distinguishing features (Table II). Patients with FACU, like patients with ACU, report having cold-induced pruritus and urticaria with the immediate onset of symptoms after cold exposure. Patients with FACU, in comparison with patients with ACU, report a younger age of onset, longer duration of disease, and atmospheric cold as a common trigger. Most importantly, patients with FACU have a positive family history and negative CSTT result. Patients with FACU, like patients with FCAS, appear to have their symptoms triggered by cold exposure, have lifelong symptoms that begin in early childhood, and have an autosomal dominant pattern of inheritance. Our data on patients with FACU suggest, however, that they have more immediate symptoms after cold exposure that are triggered by the ingestion of cold foods compared with those of patients with FCAS. Patients with FACU also do not report the fever, chills, prolonged rash, or extremity pains that are found in patients with FCAS. The proposed diagnostic criteria (Table III) help discern FACU from both ACU and FCAS. FACU should be considered in any patient who meets all 6 of the proposed diagnostic criteria (Table III). Our 20 affected participants met all of the criteria, whereas none of the unaffected subjects met any of the criteria (excluding the negative CSTT result).

Evaporative cooling appears to be a significant trigger for the development of cutaneous symptoms in patients with FACU. We assume that moist skin, when exposed to air, induces localized cutaneous cooling from the evaporation of the liquid. We suspect that a threshold temperature is reached that triggers the cutaneous symptoms in patients with FACU when their skin is moist and exposed to air (room temperature or colder). We presume a similar phenomenon occurs in patients with FACU who complain of cutaneous symptoms with handling cold objects and oropharyngeal swelling on ingestion of cold foods, in which the threshold temperature required to produce symptoms is likely warmer than that of the ice cube (CSTT). Further investigations should include effect-based temperature challenges to elicit such a threshold. Evaporative cooling testing was only performed with room temperature water and alcohol. Historically, similar reactions were observed in subjects who were exposed to warm water and room temperature air, as with bathing (Fig 2, C). Patients with FACU do not have aquagenic urticaria because there was a lack of cutaneous symptoms in our patients whose skin was both immersed in water and tested with occluded water droplets on the skin. Instead, FACU symptoms appear to be related to evaporation and cooling of the skin.

In patients with ACU, the presence of mast cell mediator release, specifically histamine and eosinophil chemotactic factor, has been documented from peripheral blood during cold challenges. Similarly, the pathogenesis of FACU is suspected
to be mast cell mediated. This is suggested by the appearance of more mast cells in the dermis in our patients at baseline with degradation after cold challenge compared with numbers seen in healthy control subjects. This correlates with the reported successful use of antihistamines for prophylaxis and treatment in some of our subjects.

No formal therapeutic trials have been performed in patients with FACU, but a reasonable initial approach includes removal from the stimulus, drying and rewarming the skin, and treatment with antihistamines. As with ACU, first-generation antihistamines, higher doses of second-generation antihistamines, or combination therapy with a leukotriene receptor antagonist might be required to control symptoms. Daily second-generation antihistamines appeared to decrease symptom severity in our patients and might be considered for prophylaxis in other patients with histamines appeared to decrease symptom severity in our patients and might be considered for prophylaxis in other patients with FACU. Patients with FACU, like patients with ACU, might be at risk of having life-threatening anaphylaxis, especially when exposed to aquatic activities. They should be advised to avoid aquatic activities and be educated on the possible need for intramuscular epinephrine. Our patients, however, suggested that their milder daily symptoms did not prevent their normal activities if they attempted to stay dry and warm. Educating family members and teachers of children on the expected symptoms of this disease is important to facilitate preparedness and avoid excessive restrictions on activity.

Limitations of this study include data collection by means of questionnaires, which might include recall bias and inaccuracies, and data collection by means of telephone, e-mail, or both. The number of subjects included in this study was small. Because of geographic constraints, personal interviews and examinations were limited. Divergences of symptom prevalence were present between families A and B. This may be due to differences in the family size, phenotypic variability, or environmental exposure. CSTTs were performed only with ice-cube contact. Although CSTT provocation time can be helpful in discerning the severity of a patient’s cold urticaria, it does not provide specific triggering temperatures.

The genetic basis for most urticarial diseases has not been elucidated. However, the identification of specific mutations in \textit{c-kit} in patients with systemic mastocytosis and identification of mutations in the NLR family, pyrin domain containing 3 gene (\textit{NLRP3}) in patients with FCAS have led to a better understanding of underlying disease processes and improved treatment. Future studies include identifying additional families, validating proposed diagnostic criteria, and implementing effect-based temperature challenges and genetic analysis.

We thank the patients and their families for participation in the studies; Dr Stanley F. Nelson and Dr Hane Lee of the University of California, Los Angeles, for helpful discussions; Dr David L. Goodman for the use of his facilities for patient examination and testing; Dr Seema S. Aceves and Dr Y. Cho for their advice on immunohistochemistry; and David Enkelis for the initial processing of the skin biopsy samples.

Clinical implications: Patients with FACU have negative CSTT results and precautions, and treatment of acute reactions of FACU is similar to treatment of ACU.

REFERENCES