

Clinical and Genetic Features of Familial Cold Urticaria: A Report of Three Families

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To the Editor: Cold urticaria (CU) accounts for 1–3% of all urticaria cases. Affected patients develop a rash and/or angioedema after physical exposure to cold agents such as cold water, air, or food. CU can be classified as an acquired or familial disorder. Familial CU (FCU) was first described in 1940. Three familial cold syndromes exist: familial delayed CU, familial cold autoinflammatory syndrome (FCAS), and familial atypical CU (FACU).^[1] Here, we report three Chinese pedigrees of FCU with an autosomal dominant inheritance pattern [Figure 1a].

Here, we report three families visiting the Department of Dermatology of Shijingshan Teaching Hospital of Capital Medical University, Beijing Shijingshan Hospital for CU from January to June 2016. The three families are of Han ethnicity, including a total of 18 individuals (11 affected and 7 unaffected). The families are not related to each other. After informed consent was obtained, the patients were evaluated for clinical characteristics associated with FCU. All affected individuals experienced urticarial rashes during childhood before 1.5 years of age, which persisted throughout life. Symptoms appeared 7 min to 2 h after exposure to cold conditions and lasted for 30 min to 4 h out of the cold environment. The urticarial rashes often appeared on the face and limbs [Figure 1b]. Fever, abdominal pain, granulomatous dermatitis, and enterocolitis were not experienced by any of the affected individuals. Angioedema (18.2%), joint pain (18.2%), and mucous membrane involvement (9.1%) were present. The cold stimulation time test (CSTT) with an ice cube was negative [Figure 1c]. C-reactive protein level and white blood cell count were normal or mildly elevated in all affected family members. The levels of serum IgM, IgG, and IgA were not reduced. Four of these patients had a medical history of allergy rhinitis and elevated total IgE, two patients had a history of vitiligo and three patients had weakly positive antinuclear antibody levels. No correlation between the occurrence of CU and the season was found in the families. The patients used antihistamine treatments irregularly, which may have diminished or relieved the patient's symptoms, but there was recurrence after withdrawal. Resolution was often facilitated by taking hot baths or resting under a warm quilt.

All affected individuals in the three families showed an autosomal dominant pattern of inheritance and physical evidence of cold-induced wheals or angioedema. These characteristics satisfy the key diagnostic features of FCU. Some presentations

of the affected individuals were clinically similar to acquired CU. However, the positive family history, early-onset, and negative CSTT results are not consistent with acquired CU syndromes. These patients are different from patients with delayed familial CU, in whom wheals appear approximately 9–18 h after cold exposure, with hyperpigmented macules.

Peripheral blood (2 ml) was obtained from each available family member and from 100 unrelated controls. Genomic DNA was extracted using a blood DNA extraction kit (Tiangen, Biotech Co., Beijing, China). Exons 1–9 of nucleotide-bind domain and leucine-rich repeat containing family pyrin-domain containing (*NLRP*) 3 gene and exon 3 of *NLRP12* were amplified by polymerase chain reaction (PCR). The primer sequences were provided by Beijing Kangso Medical Inspection Co., Ltd., China. The PCR products were sequenced using Big Dye Terminator (Applied Biosystems, Torrance, CA, USA) and ABI PRISM 3730 X1 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). cDNA of phospholipase C gamma 2 (*PLCG2*) were screened by means of PCR amplification of overlapping segments and then Sanger sequencing. Human leukocyte antigen (*HLA*)-A, B, and *DRB1* locus-specific amplification was performed using a PCR kit (Qiagen, Hilden, Germany). Exons 2, 3, and 4 for the A and B loci and exons 2 and 3 for the *DRB1* locus were sequenced in both directions using the sequence-based typing (SBT) excellerator sequence primer and Big Dye Terminator v3.1 Reaction Kit (Applied Biosystems, Torrance, CA, USA). The sequencing data were analyzed using SBT engine software (SBT excellerator, Genome Diagnostics B.V., Arnhem, the Netherlands).

Direct sequencing of the genomic PCR products revealed a synonymous mutation, c.657C>T, in exon 3 of *NLRP3* that results in the codon substitution ACC to ACT [Figure 1d]; however, this mutation would not cause an amino acid change. This mutation was carried by all affected patients in families 1 and 2 but was

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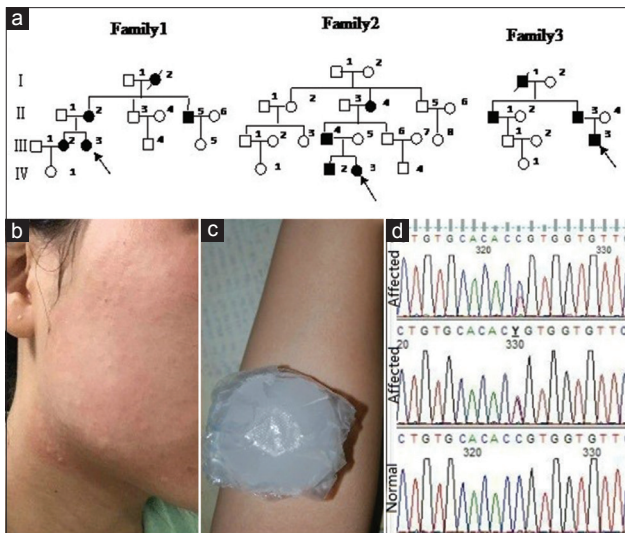


Figure 1: (a) Pedigrees of the study patients with familial cold urticaria showing an autosomal dominant inheritance pattern. (b) Erythema and wheals on the face after exposure to atmospheric cold. (c) Ice cube test performed with ice packed in thin plastic. No rash or wheal was observed. (d) A c.657C>T in exon 3 of nucleotide-bind domain and leucine-rich repeat containing family pyrin-domain containing 3 gene (*NLRP3*).

not found in unaffected family members, family 3 members, or unrelated control individuals. No mutations were detected in exon 3 of *NLRP12* or exons 1–33 of *PLCG2*. The *HLA-DRB1**07:01 allele was detected in the nine affected individuals but not in the unaffected individuals. The frequency of *HLA-DRB1**07:01 alleles in the 100 unrelated controls was not the most frequent.

NLRP3, *NLRP12*, and *NLRC4* are members of the nod-like receptor (*NLR*) family characterized by the presence of a central nucleotide-binding and oligomerization (NACHT) domain, which is commonly flanked by C-terminal leucine-rich repeats and N-terminal caspase recruitment (CARD) or pyrin (PYD) domains. The *NLR* family includes several subfamilies distinguishable by their N-terminal effect or domains.^[2] Several members of this family have been associated with auto inflammatory, autoimmune, and infectious diseases, as well as cell signaling and apoptosis. *NLRP3* mutations at chromosome 1q44 encode a protein that leads to excessive interleukin (IL)-1 β and IL-18 production and ultimately an inflammatory response. Investigators have identified more than nine mutations in exon 3 of *NLRP3* in patients with FCAS, which is characterized by periodic attacks of an urticaria-like rash, fever, conjunctivitis, and arthralgia. Interestingly, incomplete penetrance of the disease phenotype is frequently observed in individuals with a mutation in the *NLRP3* gene. Canoui *et al.*^[3] reported a polymorphism, K375E (p.Lys375Glu; c.1123A>G), in exon 3 of *NLRP3*. The affected patient presented with childhood-onset urticaria and arthralgia but never experienced fever, ocular symptoms, or hearing loss. Here, we report a synonymous *NLRP3* mutation in eight patients from two families. The mutation differs from previously identified *NLRP3* mutations in patients with FCAS. There are possible interpretations of our results including that the site of the mutation in the two families may not be in the *NLRP3* gene, or that the identified mutation may be disease causing because it alters a splice site. Further studies are required to elucidate the detailed molecular consequences of this mutation. The nucleotide structure of *NLRP12* is similar to that of *NLRP3*. The disorder caused by mutations in the *NLRP12* gene is termed as *NLRP12*-auto-inflammatory disease (*NLRP12*-AD, also

known as FCAS2) and has similar clinical phenotype with FCAS.^[4] In the literature, six causative mutations in *NLRP12* have been linked to cold induced urticaria or rash, most of the mutations are located in exon 3 of *NLRP12*. However, no mutations were detected in exon 3 of *NLRP12* in the three families examined.

FACU/*PLCG2* associated antibody deficiency and immune dysregulation (PLAID) is currently thought to be caused by deletions in *PLCG2*.^[5] PLAID is characterized by CU, autoimmunity, recurrent bacterial infection, and skin granuloma formation. Compared with reports in the literature, our patients' symptoms were not completely consistent with the symptoms of PLAID, and no antibody deficiency or granulomatous were observed. Till date, a limited number of FACU cases have been reported, with most patients being from Europe or America. The effects of race and environment on the disease are not yet known.

A few reports have described association between specific *HLA* alleles and CU. We analyzed *HLA-A* and *B* and *DRB1* in 18 members of families that included patients with FCU, and the *DRB1**07:01 phenotype was observed in the nine affected individual. This result suggests that a common genetic background may be present in some patients with FCU.

On this basis, we speculate that FCU syndromes are heterogeneous. Our report will further increase awareness of FCU. The *NLR* and *PLCG2* genes may be analyzed in mutation detection studies involving patients with FCU. *HLA* alleles might be associated with FCU morbidity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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