

Cold-induced urticarial autoinflammatory syndrome related to factor XII activation
Scheffel et al.

Supplementary Information

Table of Contents:

Supplementary Table 1

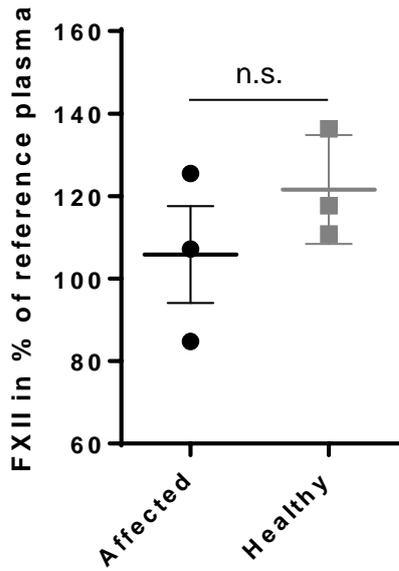
Supplementary Figures 1-4

Supplementary Table 1

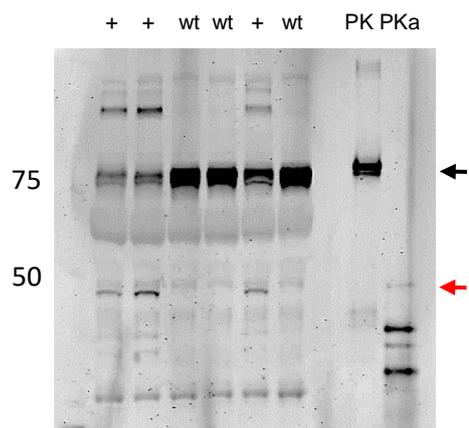
Characteristics, triggers and clinical phenotype of different cold-induced urticarial disorders

	FACAS	CAPS	FCAS 2	FCAS 3	PLAID	Acquired cold urticaria
Gene	<i>F12</i>	<i>NLRP3</i>	<i>NLRP12</i>	<i>NLRC4</i>	<i>PLCG2</i>	-
Disease triggers	Generalized exposure to cold (humid) air	Generalized exposure to cold (humid) air; Stress, infections	Generalized exposure to cold (humid) air; Stress, infections	Generalized exposure to cold (humid) air; Stress, infections	Generalized exposure to cold air; Evaporative cooling of skin; Cold water immersion	Direct skin contact with cold air, liquids or solids
Cold contact provocation tests (Ice cube/TempTest®)	Negative	Negative	Negative	Negative	Negative	Positive
Characteristics of skin lesions	Generalized wheals or erythematous papules/plaques resolving after hours	Generalized wheals or erythematous papules/plaques resolving after hours	Generalized wheals or erythematous papules/plaques resolving after hours	Generalized wheals or erythematous papules/plaques resolving after hours	Localized wheals resolving after minutes - hours; Chronic granulomatous skin lesions in few patients	Localized wheals/angioedema at sites of cold contact resolving after minutes
Skin sensations	Pruritus, burning and pain	No or only mild pruritus, burning or pain	No or only mild pruritus, burning or pain	No or only mild pruritus, burning or pain	Pruritus	Pruritus
Systemic/associated disease	Musculoskeletal involvement, chills/fever, headache, fatigue	Musculoskeletal involvement, chills/fever, headache, fatigue; Uveitis; Sensorineural hearing loss and aseptic meningitis in severe phenotypes MWS/NOMID	Musculoskeletal involvement, chills/fever, headache, fatigue	Musculoskeletal involvement, chills/fever, headache, fatigue; Gastrointestinal involvement; Macrophage activation syndrome in severe phenotypes	Autoimmune disease; Immunodeficiency; Type I allergies	None
Disease onset and course	After birth/infancy; Lifelong	After birth/infancy, rarely late-onset adulthood; Lifelong	After birth/infancy; Lifelong	After birth/infancy; Lifelong	After birth/infancy; Lifelong	Variable, any age; Spontaneous remission

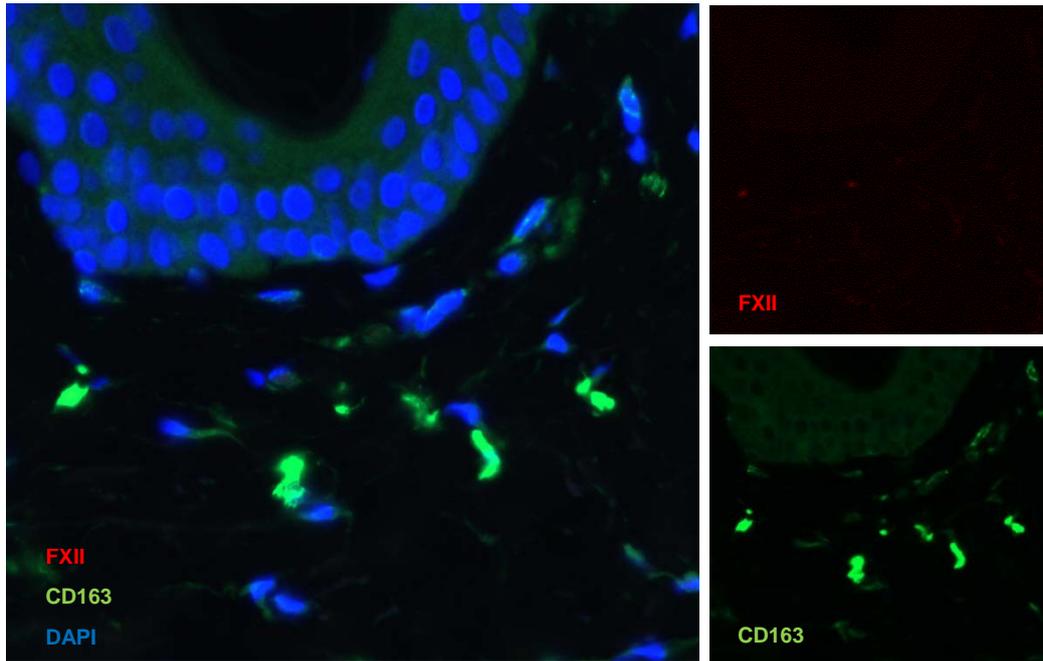
FACAS = FXII-associated cold autoinflammatory syndrome; CAPS = Cryopyrin-associated periodic syndrome; FCAS = Familial cold autoinflammatory syndrome; MWS = Muckle-Wells syndrome; NOMID = Neonatal-onset multisystem inflammatory disease; PLAID = PLCG2-associated antibody deficiency and immune dysregulation



Supplementary Figure 1: FXII plasma levels in patients are comparable to healthy controls. FXII plasma levels from FACAS (black bars) and healthy control (grey bars) subjects (n=3 affected vs. n=3 healthy) were assessed by ELISA. Graph shows individual data points and the mean \pm sem. Statistical significance was assessed by unpaired Student's t-test with Welch's correction. Source data are provided as a source data file.

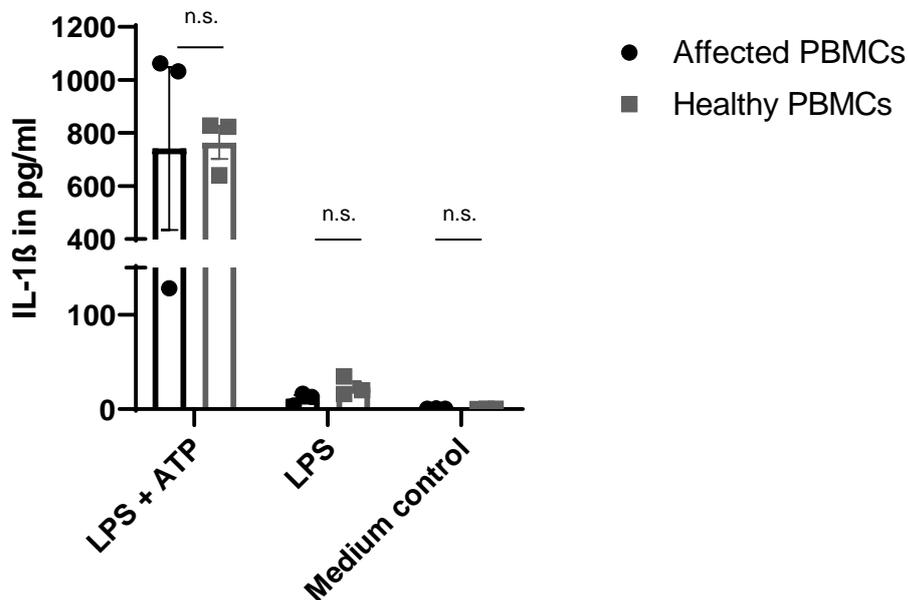


Supplementary Figure 2: Citrate plasma of affected (n=3) and healthy family members (n=3) was immunoblotted for prekallikrein (PK) showing substantial cleavage of PK (black arrow) and kallikrein (red arrow) formation when compared with activated recombinant PK, n=2 technical replicates. Source data are provided as a source data file.



Supplementary Figure 3: FXII is not expressed by skin macrophages of FACAS patients.

Lesional skin of a FACAS patient ca. 1h after cold exposure. FXII immunoreactivity does not co-localize with macrophages (green fluorescence). Original magnification 400x, n=2 technical replicates.



Supplementary Figure 4: Patient PBMCs show low basal IL-1 β secretion that is comparable to healthy controls. Peripheral blood mononuclear cells were isolated from FACAS (black bars) and healthy control (grey bars) subjects (n=3 affected vs. n=3 healthy) by density gradient centrifugation. Cells were pre-stimulated with LPS and activated by ATP, LPS-stimulated only and left untreated (medium ctrl). Bar graphs show individual data points and the mean \pm sem. Statistical significance was assessed by unpaired Student's t-test with Welch's correction. Source data are provided as a source data file.