Autoinflammatory syndromes with skin involvement

Sailesh Konda, MD[1] and Sasank Konda, BA[2]

Disease	GENE [Inheritance] Protein	Clinical manifestations	Skin findings	Treatment[1]	Miscellaneous
Familial Mediterranean Fever (FMF)	MEFV [AR] Pyrin (marenostrin)	Recurrent fevers, severe peritonitis, pleuritis, large joint arthritis, renal amyloidosis (SAA protein), splenomegaly, testicular pain	Erysipelas-like skin lesions on distal extremities; ± Henoch-Schonlein purpura, polyarteritis nodosa	Colchicine NSAIDs Analgesics Anti-TNF-α Anakinra	Most common autoinflammatory syndrome Mediterranean descent M694V mutation associated with severe disease and amyloidosis
Hyper IgD Syndrome (HIDS)	MVK [AR] Mevalonate kinase	Recurrent fevers preceded by chills/malaise ↑ IgD (> 100 UI/ml), painful cervical LAD, abdominal pain, aphthous oral/genital ulcers, HSM, athralgias, nonerosive arthritis	Erythematous macules, papules, and nodules; urticaria	Prednisone IVIG Colchicine Cyclosporine A Statins Anti-TNF-α Anakinra	Western Europeans (Netherlands, France) Triggers: vaccination, stress, trauma Mevalonate kinase is involved in cholesterol biosynthesis
TNF Receptor Associated Periodic Syndrome (TRAPS)	TNFRSF1A [AD] TNF Receptor 1	Recurrent fevers, myalgias, severe chest/abdominal/ testicular pain, LAD, periorbital edema, renal amyloidosis, oral ulcers; ↓ serum TNF R1	Erythematous patches, edematous plaques, often annular/ serpiginous, later ecchymotic	Prednisone Anti-TNF-α Anakinra	AKA Familial Hibernian fever Most common mutations are R92Q and P46L
Blau syndrome	NOD2/ CARD15 [AD] NOD2/ CARD15	Chronic granulomatous arthritis, uveitis	'Tapioca grain-like' yellowish to brown-red pinhead-sized papules	Prednisone Methotrexate Cyclosporine A Anti-TNF-α Anakinra	AKA familial juvenile systemic granulomatosis 1/3 may develop secondary glaucoma NOD2/CARD15 also involved in Crohn's disease
PAPA syndrome	PSTPIP1/ CD2BP1 [AD] PSTPIP1/ CD2BP1	**P**yogenic sterile **A**rthritis **P**yoderma gangrenosum **A**cne	Pyoderma gangrenosum, acne	Tetracycline/ Isotretinoin for acne Prednisone Anti-TNF-α Anakinra	Arthritis destroys non-axial joints (knees, elbows, ankles)
PASH syndrome	Unknown	**P**yoderma gangrenosum **A**cne **S**upprative **H**idradenitis	Pyoderma gangrenosum, acne, hidradenitis suppurativa	Anakinra	Only two patients described
Chronic Recurrent Multifocal Osteomyelitis (CRMO)	LPIN2 [AR] Lipin-2	Fever, chronic recurrent multifocal osteomyelitis (i.e. mandibular), congenital dyserythropoietic anemia	Psoriasis, palmoplantar pustulosis, acne, neutrophilic dermatitis (i.e. Sweet's syndrome)	Prednisone NSAIDs Anemia: splenectomy + blood transfusions	Major feature of Majeed syndrome
PFAPA syndrome	Unknown	**P**eriodic **F**ever **A**phthous stomatitis **P**haryngitis **A**denitis (cervical); arthritis	Rare truncal erythema, aphthous stomatitis (labial gingiva)	Prednisone Cimetidine Anakinra Tonsillectomy	AKA Marshall's syndrome Negative throat cultures required for diagnosis
Deficiency of Interleukin-1 Receptor Antagonist (DIRA)	IL1RN [AR] IL-Ra	Neonatal onset, chronic recurrent multifocal osteomyelitis, painful movement, HSM	Pustular dermatitis	Anakinra	X-ray: costal arch widening, periosteal elevation along long bones, multifocal osteolytic lesions
CANDLE syndrome	PSMB8 [AR] PSMB8	**C**hronic **A**typical **N**eutrophilic **D**ermatosis with **L**ipodystrophy and **E**levated temperature; poor growth, HSM, athralgias, basal ganglia calcifications	Annular erythematous plaques, violaceous swollen eyelids/lips, partial lipodystrophy	Prednisone Methotrexate Tacrolimus Infliximab Adalimumab Anakinra Tocilizumab	PSMB8 also involved in Nakajo-Nishimura syndrome (Japanese) and JMP (**J**oint contractures, **M**uscular atrophy, **M**icrocytic anemia, **P**anniculitis-induced lipodystrophy) syndrome

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Autoinflammatory syndromes with skin involvement (cont.)

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Cryopyrin-associated periodic syndromes (CAPS)					
Familial Cold Autoinflammatory Syndrome (FCAS)	CIAS1/NLRP3 [AD] Cryopyrin	Recurrent fevers triggered by cold with profuse sweating, drowsiness, conjunctivitis, arthralgias	Pink figurate patches or red macules/papules; not true urticaria	Anakinra Rilonacept Canakinumab Thalidomide (CINCA/NOMID)	Mildest of cryopyrinopathies
Muckle-Wells Syndrome (MWS)		Same symptoms of FCAS; NOT triggered by cold; sensorineural hearing loss, renal amyloidosis	Urticaria		AKA urticaria-deafness-amyloidosis syndrome
Chronic Infantile Neurologic Cutaneous Articular Syndrome – Neonatal Onset Multisystem Inflammatory Syndrome (CINCA/NOMID)		Distinctive facies (frontal prominence, saddle nose, facial hypoplasia), developmental delay, giant patella, polyarticular chronic inflammation, aseptic meningitis, papilledema, seizures	Urticaria		Most severe of cryopyrinopathies

[1]Anakinra = recombinant human IL-1 receptor competitive antagonist of IL-1α and IL-1β
Rilonacept = long-acting recombinant fusion protein that binds IL-1α and IL-1β and also binds the IL-1 receptor antagonist, although with a lower affinity
Canakinumab = long-acting recombinant human monoclonal antibody that binds IL-1β
Tocilizumab = recombinant human monoclonal antibody against IL-6 receptor

[AD] = Autosomal dominant; [AR] = Autosomal recessive; LAD = lymphadenopathy; HSM = hepatosplenomegaly

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