研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
八角高裕、平家俊男	家族性地中海熱	原　寿郎	小児の発熱 AtoZ	診断と治療社	東京	2012	200-204
八角高裕、平家俊男	高IgD症候群	原　寿郎	小児の発熱 AtoZ	診断と治療社	東京	2012	205-208
平家俊男	自己炎症性疾患・自然免疫不全症・近縁疾患の診断と治療	近藤直実、平家俊男	自己炎症性疾患・自然免疫不全症とその近縁疾患	診断と治療社	東京	2012	32-39
酒井秀政、平家俊男	高IgD症候群（メバロン酸キナーゼ欠乏症）	近藤直実、平家俊男	自己炎症性疾患・自然免疫不全症とその近縁疾患	診断と治療社	東京	2012	70-72
井澤和司、西小森隆太、平家俊男	クリオピリン関連周期熱症候群（CAPS）	近藤直実、平家俊男	自己炎症性疾患・自然免疫不全症とその近縁疾患	診断と治療社	東京	2012	73-77
酒井秀政、平家俊男	症例：高IgD症候群（メバロン酸キナーゼ欠乏症）	近藤直実、平家俊男	自己炎症性疾患・自然免疫不全症とその近縁疾患	診断と治療社	東京	2012	200-201
井澤和司、西小森隆太、平家俊男	症例:クリオピリン関連周期熱症候群（CAPS）	近藤直実、平家俊男	自己炎症性疾患・自然免疫不全症とその近縁疾患	診断と治療社	東京	2012	202-203
原　寿郎	免疫疾患	原寿郎/高橋孝雄/細井創	標準小児科学　第8版	医学書院	東京	2014	258-79
原　寿郎	原発性免疫不全症候群 Primary immunodeficiency syndrome	福井次矢、高木誠、小室一成	今日の治療指針 2014年版－私はこう治療している	医学書院	東京	2014	1270-1
原　寿郎	第1章:血液系疾患の医療ニーズ　第3節　原発性免疫不全症候群		希少疾患／難病の診断・治療と製品開発	(株)技術情報協会	東京	2013	593-610
原　寿郎	原発性免疫不全症候群 Primary immunodeficiency syndrome	永井良三、大田健	今日の治療と看護 改訂第3版	南江堂	東京	2012	
原　寿郎	免疫疾患	原寿郎、高橋孝雄、細井創	標準小児科学　第8版	医学書院	東京	2012	
原　寿郎	第1章：血液系疾患の医療ニーズ　第3節　原発性免疫不全症候群		希少疾患／難病の診断・治療と製品開発	(株)技術情報協会	東京	2012	593-610
原　寿郎	4.発熱の診断における自己炎症性疾患・原発性免疫不全症の位置づけ	近藤直実、平家俊男	自己炎症性疾患・自己免疫不全症とその近縁疾患	診断と治療社	東京	2012	47-52
原　寿郎	23　免疫不全	熊ノ郷淳、阪口薫雄、竹田　潔、吉田裕樹	免疫学コア講義　改訂3版	南山堂	東京	2012	234-252
原　寿郎	発熱の原因と診断	原　寿郎	小児の発熱　A to Z	診断と治療社	東京	2012	1-12
原　寿郎	その他の自己免疫・免疫関連疾患	原　寿郎	小児の発熱　A to Z	診断と治療社	東京	2012	103-105
原　寿郎	自己炎症性疾患　総論	原　寿郎	小児の発熱　A to Z	診断と治療社	東京	2012	198-199
原　寿郎	Cryopyrin-associated periodic syndrome(CAPS)	原　寿郎	小児の発熱　A to Z	診断と治療社	東京	2012	215-217
近藤直実, 大西秀典, 渡邊倫子	原発性免疫不全症の概念と分類，および自己炎症性疾患・自然免疫不全症・近縁疾患の位置付け	近藤直実，平家俊男	自己炎症性疾患・自然免疫不全症その近縁疾患	診断と治療社	東京	2012	2-31
Kanazawa, N	Rare hereditary autoinflammatory disorders		Dermatology Research Advances	NOVA Science Publishers, Inc	米国	2014	印刷中

金澤伸雄	中條−西村症候群		『日本臨床』別冊「神経症候群Ⅱ—その他の神経疾患を含めて—」	日本臨床社	東京	2014	印刷中
金澤伸雄	中條−西村症候群		自己炎症症候群の臨床	新興医学出版社	東京	2014	印刷中
金澤伸雄	誤診：アトピー性皮膚炎3. 本当は「Early-onset sarcoidosis」		皮膚科フォトクリニックシリーズ「誤診されている皮膚疾患」	メディカルレビュー社	大阪	2013	48-51
金澤伸雄	Blau症候群と若年発症サルコイドーシス		皮膚科臨床アセット14「肉芽腫性皮膚疾患 サルコイドーシス・他の肉芽腫」	中山書店	東京	2013	132-138
金澤伸雄	自己炎症疾患に対する抗IL-1療法		皮膚科サブスペシャリティーシリーズ第7巻「1冊でわかる最新皮膚科治療」	文光堂	東京	2013	176-177
金澤伸雄	中條−西村症候群の概念・病態		皮膚科臨床アセット18「紅斑症と痒疹群 フロントガイド」	中山書店	東京	2013	136-141
金澤伸雄	中條−西村症候群の診断・鑑別診断・治療		皮膚科臨床アセット18「紅斑症と痒疹群 フロントガイド」	中山書店	東京	2013	142-148
金澤伸雄	壊疽性膿皮症は自己炎症疾患か？	宮地良樹	WHAT'S NEW in 皮膚科学 2012-2013	メディカルレビュー社	大阪	2012	34-35
金澤伸雄	中條−西村症候群	原　寿郎	小児の発熱 AtoZ	診断と治療社	東京	2012	226-228
金澤伸雄	Blau症候群	長井苑子	最新医学別冊 新しい診断と治療のABC 3「サルコイドーシス(改訂第2版)」	最新医学社	大阪	2012	210-218
金澤伸雄	中條−西村症候群	近藤直実，平家俊男	自己炎症性疾患・自然免疫不全症その近縁疾患	診断と治療社	東京	2012	100-102
金澤伸雄	Case 6 中條−西村症候群	近藤直実，平家俊男	自己炎症性疾患・自然免疫不全症その近縁疾患	診断と治療社	東京	2012	210-213
上松一永	自己炎症性症候群	矢崎義雄	内科学　第10版	朝倉書店	東京	2013	1328-1330
山崎崇志、伯耆原祥、上松一永	周期性発熱、アフタ性口内炎、咽頭炎、頸部リンパ節炎(PFAPA)症候群	近藤直実、平家俊夫	自己炎症性疾患・自然免疫不全症・近縁疾患	診断と治療社	東京	2012	188-189
伯耆原祥、山崎崇志、上松一永	周期性発熱、アフタ性口内炎、咽頭炎、頸部リンパ節炎症候群（症例）	近藤直実、平家俊夫	自己炎症性疾患・自然免疫不全症・近縁疾患	診断と治療社	東京	2012	238-240
森尾友宏	第21章 先天性免疫不全症 Wiskott-Aldrich症候群	遠藤文夫	最新ガイドライン準拠 小児科診断・治療指針	中谷書店	東京	2012	840-842
森尾友宏	第19章 リウマチ性疾患 アレルギー性疾患　先天性補体欠損症　免疫不全症	赤林朗、大内尉義、黒川峰夫、小池和彦、辻省次、長瀬隆英、藤田敏郎、森屋恭爾、山本一彦、門脇孝、永井良三	カラー版内科学	西村書店	東京	2012	1333-1334
今井耕輔	第15章 原発性免疫不全	谷口　克	標準免疫学第三版	医学書院	東京	2013	392-433

雑誌（英文）

発表者名	論文タイトル名	発表雑誌	巻号	ページ	出版年
Abe J, Nakamura K, Nishikomori R, Kato M, Mitsuiki N, Izawa K, Awaya T, Kawai T, Yasumi T, Toyoshima I, Hasegawa K, Ohshima Y, Hiragi T, Sasahara Y, Suzuki Y, Kikuchi M, Osaka H, Ohya T, Ninomiya S, Fujikawa S, Akasaka M, Iwata N, Kawakita A, Funatsuka M, Shintaku H, Ohara O, Ichinose H, Heike T.	A nationwide survey of Aicardi-Goutieres syndrome patients identifies a strong association between dominant TREX1 mutations and chilblain lesions: Japanese cohort study.	Rheumatology		in press	
Nakagawa K, Gonzalez-Roca E, Souto A, Kawai T, Umebayashi H, Campistol JM, Cañellas J, Takei S, Kobayashi N, Callejas-Rubio JL, Ortego-Centeno N, Ruiz-Ortiz E, Rius F, Anton J, Iglesias E, Jimenez-Treviño S, Vargas C, Fernandez-Martin J, Calvo I, Hernández-Rodríguez J, Mendez M, Dordal MT, Basagaña M, Bujan S, Yashiro M, Kubota T, Koike R, Akuta N, Shimoyama K, Iwata N, Saito MK, Ohara O, Kambe N, Yasumi T, Izawa K, Kawai T, Heike T, Yagüe J, Nishikomori R, Aróstegui JI.	Somatic NLRP3 mosaicism in Muckle-Wells syndrome. A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes.	Ann Rheum Dis.		in press	
Kawai M, Yoshikawa T, Nishikomori R, Heike T, Takahashi K.	Obvious optic disc swelling in a patient with cryopyrin-associated periodic syndrome	Clin Ophthalmol	7	1581-5	2013
Yoshioka T, Nishikomori R, Hara J, Okada K, Hashii Y, Okafuji I, Nodomi S, Kawai T, Izawa K, Ohnishi H, Yasumi T, Nakahata T, Heike T.	Autosomal dominant anhidrotic ectodermal dysplasia with immunodeficiency caused by a novel NFKBIA mutation, p.Ser36Tyr, presents with mild ectodermal dysplasia and non-infectious systemic inflammation.	J Clin Immunol.	33(7)	1165-74	2013
Taniuchi S, Nishikomori R, Iharada A, Tuji S, Heike T, Kaneko K.	MEFV Variants in Patients with PFAPA Syndrome in Japan.	Open Rheumatol J.	19(7)	22-25	2013
Yanagimachi MD, Niwa A, Tanaka T, Honda-Ozaki F, Nishimoto S, Murata Y, Yasumi T, Ito J, Tomida S, Oshima K, Asaka I, Goto H, Heike T, Nakahata T, Saito MK.	Robust and highly-efficient differentiation of functional monocytic cells from human pluripotent stem cells under serum- and feeder cell-free conditions.	PLoS One	8(4)	e59243	2013
Imagawa T, Nishikomori R, Takada H, Takeshita S, Patel N, Kim D, Lheritier K, Heike T, Hara T, Yokota S.	Safety and efficacy of canakinumab in Japanese patients with phenotypes of cryopyrin-associated periodic syndrome as established in the first open-label, phase-3 pivotal study (24-week results).	Clin Exp Rheumatol.	31(2)	302-9	2013
Yokota S, Nishikomori R, Takada H, Kikuchi M, Nozawa T, Kanetaka T, Kizawa T, Miyamae T, Mori M, Heike T, Hara T, Imagawa T.	Guidance on the use of canakinumab in patients with cryopyrin-associated periodic syndrome in Japan.	Mod Rheumatol.	23(3)	425-9	2013
Abe J, Izawa K, Nishikomori R, Awaya T, Kawai T, Yasumi T, Hiragi N, Hiragi T, Ohshima Y, Heike T.	Heterozygous TREX1 p.Asp18Asn mutation can cause variable neurological symptoms in a family with Aicardi-Goutieres syndrome/familial chilblain lupus.	Rheumatology (Oxford)	52(2)	406-408	2013
Tanaka T, Takahashi K, Yamane M, Tomida S, Nakamura S, Oshima K, Niwa A, Nishikomori R, Kambe N, Hara H, Mitsuyama M, Morone N, Heuser JE, Yamamoto T, Watanabe A, Sato-Otsubo A, Ogawa S, Asaka I, Heike T, Yamanaka S, Nakahata T, Saito MK.	Induced pluripotent stem cells from CINCA syndrome patients as a model for dissecting somatic mosaicism and drug discovery.	Blood	120(6)	1299-1308	2012
Kawai T, Nishikomori R, Heike T.	Diagnosis and treatment in anhidrotic ectodermal dysplasia with immunodeficiency.	Allergol Int.	61(2)	207-217	2012
Hiejima E, Yasumi T, Kubota H, Ohmori K, Ohshima K, Nishikomori R, Nakase H, Chiba T, Heike T.	Gastric ulcer and gastroenteritis caused by Epstein-Barr virus during immunosuppressive therapy for a child with systemic juvenile idiopathic arthritis.	Rheumatology (Oxford)	51(11)	2107-2109	2012
Tsumura M, Okada S, Sakai H, Yasunaga S, Ohtsubo M, Murata T, Obata H, Yasumi T, Kong XF, Abhyankar A, Heike T, Nakahata T, Nishikomori R, Al-Muhsen S, Boisson-Dupuis S, Casanova JL, Alzahrani M, Shehri MA, Elghazali G, Takihara Y, Kobayashi M.	Dominant-negative STAT1 SH2 domain mutations in unrelated patients with Mendelian susceptibility to mycobacterial disease.	Hum Mutat.	33(9)	1377-1387	2012
Kawai T, Nishikomori R, Izawa K, Murata Y, Tanaka N, Sakai H, Saito M, Yasumi T, Takaoka Y, Nakahata T, Mizukami T, Nunoi H, Kiyohara Y, Yoden A, Murata T, Sasaki S, Ito E, Akutagawa H, Kawai T, Imai C, Okada S, Kobayashi M, Heike T.	Frequent somatic mosaicism of NEMO in T cells of patients with X-linked anhidrotic ectodermal dysplasia with immunodeficiency.	Blood	119(23)	5458-5466	2012
Kawai T, Saito M, Nishikomori R, Yasumi T, Izawa K, Murakami T, Okamoto S, Mori Y, Nakagawa N, Imai K, Nonoyama S, Wada T, Yachie A, Ohmori K, Nakahata T, Heike T.	Multiple reversions of an IL2RG mutation restore T cell function in an X-linked severe combined immunodeficiency patient.	J Clin Immunol.	32(4)	690-697	2012
Izawa K, Hijikata A, Tanaka N, Kawai T, Saito MK, Goldbach-Mansky R, Aksentijevich I, Yasumi T, Nakahata T, Heike T, Nishikomori R, Ohara O.	Detection of base substitution-type somatic mosaicism of the NLRP3 gene with >99.9% statistical confidence by massively parallel sequencing.	DNA Res.	19(2)	143-152	2012
Kutsuna S, Ohmagari N, Tanizaki R, Hagino N, Nishikomori R, Ujiie M, Takeshita N, Hayakawa K, Kato Y, Kanagawa S.	The first case of adult-onset PFAPA syndrome in Japan.	Mod Rheumatol.		in press	
Shinar Y, Obici L, Aksentijevich I, Bennetts B, Austrup F, Ceccherini I, Costa JM, De Leener A, Gattorno M, Kania U, Kone-Paut I, Lezer S, Livneh A, Moix I, Nishikomori R, Ozen S, Phylactou L, Risom L, Rowczenio D, Sarkisian T, van Gijn ME, Witsch-Baumgartner M, Morris M, Hoffman HM, Touitou I; European Molecular Genetics Quality Network.	Guidelines for the genetic diagnosis of hereditary recurrent fevers.	Ann Rheum Dis.	71(10)	1599-1605	2012

Mizuno T, Sakai H, Nishikomori R, Oshima K, Ohara O, Hata I, Shigematsu Y, Ishige T, Tamura K, Arakawa H	Novel mutations of MVK gene in Japanese family members affected with hyperimmunoglobulinemia D and periodic fever syndrome.	Rheumatol Int	32(12)	3761-3764	2012
Aoyama K, Amano H, Takaoka Y, Nishikomori R, Ishikawa O	Cryopyrin-associated periodic syndrome: a case report and review of the Japanese literature.	Acta Derm Venereol	92(4)	395-398	2012
Hiejima E, Komatsu H, Takeda Y, Sogo T, Inui A, Okafuji I, Nishikomori R, Nakahata T, Fujisawa T.	Acut liver failure in young children with systemic-onset juvenile idiopathic arthritis without macrophage activation syndrome: Report of two cases.	J. Pediatr. Child Health	48	E122-125	2012
Ohnishi H, Teramoto T, Iwata H, Kato Z, Kimura T, Kubota K, Nishikomori R, Kaneko H, Seishima M, Kondo N	Characterization of NLRP3 variants in Japanese cryopyrin-associated periodic syndrome patients.	J Clin Immunol.	32(2)	221-229	2012
Ninomiya T, Takada H, Nagatomo Y, Nanishi E, Nagata H, Yamamura K, Doi T, Ikeda I, Hara T	Development of Kawasaki disease in a patient with PFAPA	Pediatrics International	55(6)	801-2	2013
Higuchi Y, Shimizu J, Hatanaka M, Kitano E, Kitamura H, Takada H, Ishimura M, Hara T, Ohara O, Asagoe K, Kubo T	The identification of a novel splicing mutation in C1qB in a Japanese family with C1q deficiency: a case report.	Pediatr Rheumatol Online J.	11(1)	41	2013
Obinata K, Lee T, Niizuma T, Kinoshita K, Shimizu T, Hoshina T, Sasaki Y, Hara T	Two cases of partial dominant interferon-γ receptor 1 deficiency that presented with different clinical courses of bacille Calmette-Guérin multiple osteomyelitis.	J Infect Chemother	19(4)	757-60	2013
Nozaki T, Takada H, Ishimura M, Ihara K, Imai K, Morio T, Kobayashi M, Nonoyama S, Hara T	Endocrine complications in primary immunodeficiency diseases in Japan.	Clin Endocrinol(Oxf)	77	628-634	2012
Kusuhara K, Hoshina T, Saito M, Ishimura M, Inoue H, Horiuchi T, Sato T, Hara T	Successful treatment of a patient with tumor necrosis factor receptor-associated periodic syndrome using a half-dose ofetanercept.	Pediatr Int	54	552-555	2012
Hoshina T, Kusuhara K, Saito M, Mizuno Y, Hara T	NKRP1A+ γδ and αβ T cells are preferentially induced in patients with Salmonella infection.	Hum Immunol	73	623-628	2012
Yamamura K, Ihara K, Ikeda K, Nagata H, Mizuno Y, Hara T	Histo-blood group gene polymorphisms as potential genetic modifiers of the development of coronary artery lesions in patients with Kawasaki disease.	Int J Immunogenet	39(2)	119-125	2012
Onoyama S, Ihara K, Yamaguchi Y, Ikeda K, Yamaguchi K, Yamamura K, Hoshina T, Mizuno Y, Hara T	Genetic susceptibility to Kawasaki disease: analysis of pattern recognition receptor genes.	Hum Immunol	73	654-660	2012
Shiraishi A, Ohga S, Doi T, Ishimura M, Takimoto T, Takada H, Miyamoto T, Abe Y, Hara T	Treatment choice of immunotherapy or further chemotherapy for Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis.	Pediatr Blood Cancer	59	265-270	2012
Kitajima J, Inoue H, Ohga S, Kinjo T, Ochiai M, Yoshida T, Kusuhara K, Hara T	Differential transmission and postnatal outcome in triplets with congenital cytomegalovirus infection.	Pediatr Development Patho	15	151-155	2012
Yokota S, Imagawa T, Mori M, Miyamae T, Takei S, Iwata N, Umebayashi H, Murata T, Miyoshi M, Tomiita M, Nishimoto N, Kishimoto T.	Long-term treatment of systemic juvenile idiopathic arthritis with tocilizumab: results of an open-label extension study in Japan.	Ann Rheum Dis	72(4)	627-8	2013
Inaba Y, Ozawa R, Aoki C, Imagawa T, Mori M, Hara R, Miyamae T, Saito T, Yokota S	Radiologic analysis of the effect of tocilizumab on hands and large joints in children with systemic juvenile idiopathic arthritis.	Mod Rheumatol	23(4)	667-73	2013
Imagawa T, Takei S, Umebayashi H, Yamaguchi K, Itoh Y, Kawai T, Iwata N, Murata T, Okafuji I, Miyoshi M, Onoe Y, Kawano Y, Kinjo N, Mori M, Mozaffarian N, Kupper H, Santra S, Patel G, Kawai S, Yokota S	Efficacy, pharmacokinetics, and safety of adalimumab in pediatric patients with juvenile idiopathic arthritis in Japan.	Clin Rheumatol	31(12)	1713-1721	2012
Yuzurihara SS, Ao K, Hara T, Tanaka F, Mori M, Kikuchi N, Kai S, Yokota S	Human parechovirus-3 infection in nine neonates and infants presenting symptoms of hemophagocytic lymphohistiocytosis.	J Infect Chemother	19(1)	144-148	2012
Shinoki T, Hara R, Kaneko U, Miyamae T, Imagawa T, Mori M, Yokota S	Safety and response to influenza vaccine in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab.	Mod Rheumatol	22(6)	871-876	2012
Yamamoto T, Tsutsumi N, Tochio H, Ohnishi H, Kubota K, Kato Z, Shirakawa M, Kondo N.	Functional assessment of the mutational effects of human IRAK4 and MyD88 genes.	Mol Immunol		in press	
Ebisawa M, Nishima S, Ohnishi H, Kondo N.	Pediatric allergy and immunology in Japan.	Pediatr Allergy Immunol	24	704-14	2013
Kubota K, Ohnishi H, Teramoto T, Matsui E, Murase K, Kanoh H, Kato Z, Kaneko H, Seishima M, Kondo N.	In Vitro Analysis of the Functional Effects of an NLRP3 G809S Variant with the co-Existence of MEFV Haplotype Variants in Atypical Autoinflammatory Syndrome.	J Clin Immunol	33(2)	325-34	2013
Ohnishi H, Miyata R, Suzuki T, Nose T, Kubota K, Kato Z, Kaneko H, Kondo N.	A raipd screening method to detect autosomal-dominant ectodermal dysplasia with immune deficiency syndrome.	J Allergy Clin Immunol	129	578-580	2012
Nada M, Ohnishi H, Tochio H, Kato Z, Kimura T, Kubota K, Yamamoto T, Kamatari Y, Tsutsumi N, Shirakawa M, Kondo N.	Morecular analysis of the binding mode of Toll/interleukin-1 receptor (TIR) domain proteins during TLR2 signaling.	Mol Immunol	52	108-116	2012
Ohnishi H, Tochio H, Kato Z, Kawamoto N, Kimura T, Kubota K, Yamamoto T, Funasaka T, Nakano H, Wong RW, Shirakawa M, Kondo N.	TRAM is involved in IL-18 signaling and functions as a sorting adaptor for MyD88.	PLoS One	7	e38423	2012
Hori T, Ohnishi H, Teramoto T, Tsubouchi K, Naiki T, Hirose Y, Ohara O, Seishima M, Kaneko H, Fukao T, Kondo N.	Autosomal-Dominant Chronic Mucocutaneous Candidiasis with STAT1-Mutation can be Complicated with Chronic Active Hepatitis and Hypothyroidism.	J Clin Immunol	32	1213-20	2012

Migita K, Agematsu K, Masumoto J, Ida H, Honda S, Jiuchi Y, Izumi Y, Maeda Y, Uehara R, Nakamura Y, Koga T, Kawakami A, Nakashima M, Fujieda Y, Nonaka F, Eguchi K, Furukawa H, Nakamura T,Nakamura M, Yasunami M	The contribution of SAA1 polymorphisms to Familial Mediterranean fever susceptibility in the Japanese population.	PLoS One	8(2)	e55227	2013
Migita K, Uehara R, Nakamura Y, Yasunami M, Tsuchiya-Suzuki A, Yazaki M, Nakamura A, Masumoto J, Yachie A, Furukawa H, Ishibashi H, Ida H, Yamazaki K, Kawakami A, Agematsu K	Familial Mediterranean Fever in Japan.	Medicine (Baltimore)	91	337-343	2012
Migita K, Ida H, Moriuchi H, Agematsu K	Clinical relevance of MEFV gene mutations in Japanese patients with unexplained fever.	J Rheumatol	39	875-877	2012
Kita J, Tamai M, Arima K, Nakashima Y, Suzuki T, Kawashiri SY, Iwamoto N, Okada A, Koga T, Yamasaki S, Nakamura H, Origuchi T, Ida H, Aoyagi K, Uetani M, Eguchi K, Kawakami A	Treatment discontinuation in patients with very early rheumatoid arthritis in sustained simplified disease activity index remission after synthetic disease-modifying anti-rheumatic drug administration.	Mod Rheumatol	22	346-352	2012
Kita J, Tamai M, Arima K, Nakashima Y, Suzuki T, Kawashiri SY, Okada A, Koga T, Yamasaki S, Nakamura H, Origuchi T, Aramaki T, Nakashima M, Fujikawa K, Tsukada T, Ida H, Aoyagi K, Uetani M, Eguchi K, Kawakami A	Delayed treatment with tumor necrosis factor inhibitors in incomplete responders to synthetic disease-modifying anti-rheumatic drugs shows an excellent effect in patients with very early rheumatoid arthritis with poor prognosis factors.	Mod Rheumatol	22	195-201	2012
Hida A, Akahoshi M, Takagi Y, Imaizumi M, Sera N, Soda M, Maeda R, Nakashima E, Ida H, Kawakami A, Nakamura T, Eguchi K	Lipid infiltration in the parotid glands: a clinical manifestation of metabolic syndrome.	Exp Clin Endocrinol Diabetes	120	110-115	2012
Ichinose K, Origuchi T, Kawashiri SY, Iwamoto N, Fujikawa K, Aramaki T, Kamachi M, Arima K, Tamai M, Nakamura H, Ida H, Kawakami A, Eguchi K	Long-term follow-up of adalimumab monotherapy for rheumatoid arthritis in Japanese patients: a report of six cases.	Rheumatol Int	32	483-487	2012
Tamai M, Kawakami A, Uetani M, Fukushima A, Arima K, Fujikawa K, Iwamoto N, Aramaki T, Kamachi M, Nakamura H, Ida H, Origuchi T, Aoyagi K, Eguchi K	Magnetic resonance imaging (MRI) detection of synovitis and bone lesions of the wrists and finger joints in early-stage rheumatoid arthritis: comparison of the accuracy of plain MRI-based findings and gadolinium-diethylenetriamine pentaacetic acid-enhanced MRI-based findings.	Mod Rheumatol	22	654-658	2012
Satoh T, Kambe N, Matsue H	NLRP3 activation induces ASC-dependent programmed necrotic cell death, which leads to neutrophilic inflammation.	Cell Death Dis.	4	e644	2013
Ikeda K, Kambe N, Satoh T, Matsue H, Nakajima H	Preferentially inflamed tendon sheaths in the swollen but not tender joints in a 5-year-old boy with Blau syndrome.	J Pediatr.	163	1525. e1	2013
Kanazawa N, Tchernev G, Kambe N	Monogenic early-onset sarcoidosis is no longer a variant of "idiopathic" sarcoidosis.	J Am Acad Dermatol.	69	164-5	2013
Nakamura Y, Kambe N	Linkage of bacterial colonization of skin and the urticaria-like rash of NLRP3-mediated autoinflammatory syndromes through mast cell-derived TNF-α.	J Dermatol Sci.	71	83-8	2013
Nakamura Y, Franchi L, Kambe N, Meng G, Strober W, Núñez G	Critical role for mast cells in interleukin-1β-driven skin inflammation associated with an activating mutation in the Nlrp3 protein.	Immunity	37	85-95	2012
Kanazawa N	Hereditary disorders presenting with urticaria.	Immunol Allergy Clin N Am,	34	169-179	2014
Kunimoto K, Kimura A, Uede K, Okuda M, Aoyagi N, Furukawa F, Kanazawa N	A new infant case of Nakajo-Nishimura syndrome with a genetic mutation in the immunoproteasome subunit: an overlapping entity with JMP and CANDLE syndrome related to PSMB8 mutations.	Dermatology	227	26-30	2013
Kanazawa N	Comprehensive review of rare hereditary autoinflammatory disorders.	J Genet Disor Genet Rep	2(2)	1000106	2013
Kanazawa N	Rare hereditary autoinflammatory disorders: towards an understanding of critical in vivo inflammatory pathways	J Dermatol Sci	66	183-189	2012
Kanazawa N	Nakajo-Nishimura syndrome: an autoinflammatory disorder showing pernio-like rashes and progressive partial lipodystrophy	Allergol Int	61	197-206	2012
Tchernev G, Ananiev J, Cardoso JC, Wollina U, Verma SB, Patterson JW, Dourmishev LA, Tronnier M, Okamoto H, Mizuno K, Kanazawa N, Gulubova M, Manolova I, Salaro C	Sarcoidosis and molecular mimicry—important etiopathogenetic aspects: current state and future directions	Wien Klin Wochenschr	124	227-238	2012
Ikeda T, Kanazawa N, Furukawa F	Hydroxychloroquine administration for Japanese lupus erythematosus in Wakayama: A pilot study	J Dermatol	39	531-535	2012
Kuwahara J, Li HJ, Kanazawa N, Furukawa F	Attempts to induce auricular hematoma in a mouse model of collagen-induced arthritis	Aesthet Dermatol	22	118-123	2012
Shigemura T, Nakazawa Y, Yoshikawa K, Hirabayashi K, Saito S, Kobayashi N, Sakashita K, Shiohara M, Wada T, Shimodaira S, Agematsu K, Koike K.	Successful cord blood transplantation after repeated transfusions of unmobilized neutrophils in addition to antifungal treatment in an infant with chronic granulomatous disease complicated by invasive pulmonary aspergillosis.	Transfusion		in press	
Sugiyama R, Agematsu K, Migita K, Nakayama J, Mokuda S, Ogura F, Haraikawa K, Okumura C, Suehiro S, Morikawa S, Ito Y, Masumoto J.	Defect of suppression of inflammasome-independent interleukin-8 secretion from SW982 synovial sarcoma cells by familial Mediterranean fever-derived pyrin mutations.	Mol Biol Rep.	41(1)	545-53	2014
Yamazaki K, Kawashima H, Sato S, Tsunoda H, Yoshimura Y, Higuchi M, Hokibara S, Yamazaki T, Agematsu K	Increased CD45RO(+) CD62L(+) CD4(+) T-cell subpopulation responsible for Th2 response in Kimura's disease.	Hum Immunol.	74	1097-1102	2013
Wada T, Muraoka M, Toma T, Imai T, Shigemura T, Agematsu K, Haraguchi K, Moriuchi H, Oh-Ishi T, Kitoh T, Ohara O, Morio T, Yachie A.	Rapid Detection of Intracellular p47phox and p67phox by Flow Cytometry; Useful Screening Tests for Chronic Granulomatous Disease.	J Clin Immunol.	33	857-864	2013

Wada T, Toga A, Sakakibara Y, Toma T, Shigemura T, Agematsu K, Yachie A	Clonal expansion of Epstein-Barr virus (EBV)-infected γδ T cells in patients with chronic active EBV disease and hydroa vacciniforme-like eruptions.	Int J Hematol	96(4)	443-9	2012
Wada T, Kanegane H, Ohta K, Katoh F, Imamura T, Nakazawa Y, Miyashita R, Hara J, Hamamoto K, Yang X, Filipovich AH, Marsh RA, Yachie A	Sustained elevation of serum interleukin-18 and its association with hemophagocytic lymphohistiocytosis in XIAP deficiency.	Cytokine	65(1)	74-8	2014
Shimizu M, Nakagishi Y, Yachie A	Distinct subsets of patients with systemic juvenile idiopathic arthritis based on their cytokine profiles.	Cytokine	61(2)	345-8	2013
Shimizu M, Yokoyama T, Tokuhisa Y, Ishikawa S, Sakakibara Y, Ueno K, Yachie A	Distinct cytokine profile in juvenile systemic lupus erythematosus-associated macrophage activation syndrome.	Clin Immunol.	146(2)	73-6	2013
Ishikawa S, Shimizu M, Ueno K, Sugimoto N, Yachie A	Soluble ST2 as a marker of disease activity in systemic juvenile idiopathic arthritis.	Cytokine	62(2)	272-7	2013
Wada T, Sakakibara Y, Nishimura R, Toma T, Ueno Y, Horita S, Tanaka T, Nishi M, Kato K, Yasumi T, Ohara O, Yachie A	Down-regulation of CD5 expression on activated CD8(+) T cells in familial hemophagocytic lymphohistiocytosis with perforin gene mutations.	Hum Immunol.	74	1579-1585	2013
Shimizu M. Kanegane H. Wada T. Motoyoshi Y. Morio T. Candotti F. Yachie A	Aberrant glycosylation of IgA in Wiskott-Aldrich syndrome and X-linked thrombocytopenia.	J Allergy Clin Immunol.	131(2)	587-590.e3	2013
Nakaoka H, Kanegane H, Taneichi H, Miya K, Yang X, Nomura K, Takezaki S, Yamada M, Ohara O, Kamae C, Imai K, Nonoyama S, Wada T, Yachie A, Hershfield MS, Ariga T, Miyawaki T.	Delayed onset adenosine deaminase deficiency associated with acute disseminated encephalomyelitis.	Int J Hematol	95	692-696	2012
Shimizu M, Yachie A	Compensated inflammation in systemic juvenile idiopathic arthritis: role of alternatively activated macrophages.	Cytokine	60	226-232	2012
Shimizu M, Nakagishi Y, Kasai K, Yamasaki Y, Miyoshi M, Takei S, Yachie A.	Tocilizumab masks the clinical symptoms of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome: the diagnostic significance of interleukin-18 and interleukin-6.	Cytokine	58(2)	287-294	2012
Iwata K, Toma T, Yachie A	38-year-old woman with recurrent abdominal pain, but no fever.	Int J Gen Med	5	265-268	2012
Fukuda S, Nanki T, Morio T, Hasegawa H, Koike R, Miyasaka N	Recurrent mitral valve regurgitation with neutrophil infiltration in a patient with multiple aseptic abscesses.	Mod Rheumatol.		in press	
Miyabe C, Miyabe Y, Miura NN, Takahashi K, Terashima Y, Morio T, Yamagata N, Ohno N, Shudo K, Suzuki J-I, Isobe M, Matsuhima K, Tsuboi R, Miyasaka N, and Nanki T.	Am80, a retinoic acid receptor agonist, ameliorates murine vasculitis through the suppression of neutrophil migration and activation.	Arthritis Rheumatism.	65	503-512	2013
Park TY, Kim SH, Shin YC, Lee NH, Lee RK, Shim JH, Glimcher LH, Mook-Jung I, Cheong E, Kim WK, Honda F, Morio T, Lim JS, Lee SK.	Amelioration of neurodegenerative diseases by cell death-induced cytoplasmic delivery of humanin.	J Control Release.	166	307-315	2013
Isoda T, Mitsuiki N, Ohkawa T, Kaneko S, Endo A, Ono T, Aoki Y, Tomizawa D, Kajiwara M, Araki S, Nagasawa M, Morio T, Takagi M, Mizutani S.	Irreversible Leukoencephalopathy After Reduced-intensity Stem Cell Transplantation in a Dyskeratosis Congenita Patient With TINF2 Mutation.	J Pediatr Hematol Oncol	35	e178-82	2013
Kamae C, Nakagawa N, Sato H, Honma K, Mitsuiki N, Ohara O, Kanegane H, Pasic S, Pan-Hammarström Q, van Zelm MC, Morio T, Imai K, Nonoyama S	Common variable immunodeficiency classification by quantifying T-cell receptor and immunoglobulin κ-deleting recombination excision circles.	J Allergy Clin Immunol	131(5)	1437-40.e5	2013
Yoshimi A. Kamachi Y. Imai K. Watanabe N. Nakadate H. Kanazawa T. Ozono S. Kobayashi R. Yoshida M. Kobayashi C. Hama A. Muramatsu H. Sasahara Y. Jakob M. Morio T. Ehl S. Manabe A. Niemeyer C. Kojima S.	Wiskott–Aldrich syndrome presenting with a clinical picture mimicking juvenile myelomonocytic leukaemia.	Pediatr Blood Cancer	60	836-41	2013
Kawasaki Y, Toyoda H, Otsuki S, Iwasa T, Iwamoto S, Azuma E, Itoh-Habe N, Wada H, Fujimura Y, Morio T, Imai K, Mitsuiki N, Ohara O, Komada Y.	A novel Wiskott-Aldrich syndrome protein mutation in an infant with thrombotic thrombocytopenic purpura.	Eur J Haematol	90	164-168	2012
Isoda T. Takagi M. Piao J. Nishii R. Masaki S. Masuda K. Ikawa T. Azuma M. Morio T. Kawamoto H. Mizutani S.	Process for immune defect and chromosomal translocation during early thymocyte development lacking ATM.	Blood	120	789-799	2012
Honda F. Kano H. Kanegane H. Nonoyama S. Kim E-S. Lee S-K. Takagi M. Mizutani S. Morio T.	Btk negatively regulates ROS production and stimulation-induced apoptosis in human neutrophils.	Nature Immunol	13	369-378	2012
Kuramitsu M. Sato-Otsubo A. Morio T. Takagi M. Toki T. Terui K. RuNan W. Kanno H. Ohga S. Ohara A. Kojima S. Kitoh T. Goi K. Kudo K. Matsubayashi T. Mizue N. Ozeki M. Masumi A. Momose H. Takizawa K. Mizukami T. Yamaguchi K. Ogawa S. Ito E.	Extensive gene deletions in Japanese patients with Diamond–Blackfan anemia.	Blood	119	2376-2384	2012
Sato R. Iiizumi S. Kim E-S. Honda F. Lee S-K. Adachi N. Koyama H. Mizutani S. Morio T.	Impaired cell adhesion, apoptosis, and signaling in WASP-gene disrupted Nalm-6 pre-B cells and recovery of cell adhesion using a transducible form of WASp.	Int J Hematol	95	299-310	2012
Kojima R, Ohno T, Iikura M, Niki T, Hirashima M, Iwaya K, Tsuda H, Nonoyama S, Matsuda A, Saito H, Matsumoto K, Nakae S	Galectin-9 enhances cytokine secretion, but suppresses survival and degranulation, in human mast cell line.	PLoS One	9(1)	e86106	2014
Rawat A, Singh S, Suri D, Gupta A, Saikia B, Minz RW, Sehgal S, Vaiphei K, Kamae C, Honma K, Nakagawa N, Imai K, Nonoyama S, Oshima K, Mitsuiki N, Ohara O, Chan KW, Lau YL	Chronic Granulomatous Disease: Two Decades of Experience From a Tertiary Care Centre in North West India.	J Clin Immunol.	34(1)	58-67	2014
Bousfiha AA, Jeddane L, Ailal F, Al Herz W, Conley ME, Cunningham-Rundles C, Etzioni A, Fischer A, Franco JL, Geha RS, Hammarström L, Nonoyama S, Ochs HD, Roifman CM, Seger R, Tang ML, Puck JM, Chapel H, Notarangelo LD, Casanova JL.	A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside.	J Clin Immunol	33(6)	1078-87	2013

Kakiuchi S, Nonoyama S, Wakamatsu H, Kogawa K, Wang L, Kinoshita-Yamaguchi H, Takayama-Ito M, Lim CK, Inoue N, Mizuguchi M, Igarashi T, Saijo M	Neonatal herpes encephalitis caused by a virologically confirmed acyclovir-resistant herpes simplex virus 1 strain.	J Clin Microbiol	51(1)	356-9	2013
Ma CS, Avery DT, Chan A, Batten M, Bustamante J, Boisson-Dupuis S, Arkwright PD, Minegishi Y, Nonoyama S, French MA, Choo S, Peake J, Wong M, Cook MC, Fulcher DA, Casanova JL, Deenick EK, Tangye SG.	Functional STAT3 deficiency compromises the generation of human T follicular helper cells.	Blood	26;119	3997-4008	2012
Ishida H, Imai K, Homma K, Tamura S, Imamura T, Itoh M, Nonoyama S	GATA-2 anomaly and clinical phenotype of a sporadic case of lymphedema, dendritic cell, monocyte, B- and NK-cell (DCML) deficiency, and myelodysplasia.	Eur J Pediatr	171	1273-1276	2012
Suri D, Singh S, Rawat A, Gupta A, Kamae C, Honma K, Nakagawa N, Imai K, Nonoyama S, Oshima K, Mitsuiki N, Ohara O, Bilhou-Nabera C, Proust A, Ahluwalia J, Dogra S, Saikia B, Walker Minz R, Sehgal S.	Clinical profile and genetic basis of Wiskott-Aldrich syndrome at Chandigarh, north India.	Asian Pac J Allergy Immunol	30	71-78	2012
Yang X, Kanegane H, Nishida N, Imamura T, Hamamoto K, Miyashita R, Imai K, Nonoyama S, Sanayama K, Yamaide A, Kato F, Nagai K, Ishii E, Zelm M, Latour S, Zhao X, Miyawaki T.	Clinical and genetic characteristics of XIAP deficiency in Japan.	J Clin Immunol	32	411-420	2012
Saito Y, Kagami SI, Sanayama Y, Ikeda K, Suto A, Kashiwakuma D, Furuta S, Iwamoto I, Nonaka K, Ohara O, Nakajima H	AT-rich interactive domain-containing protein 5a functions as a negative regulator of RORγt-induced Th17 cell differentiation.	Arthritis Rheum.		in press	
Lee YW, Yang EA, Kang HJ, Yang X, Mitsuiki N, Ohara O, Miyawaki T, Kanegane H, Lee JH	Novel mutation of IL2RG gene in a Korean boy with X-linked severe combined immunodeficiency	J Investig Allergol Clin Immunol.	23	65-67	2013
Suzuki J, Kuwahara M, Tofukuji S, Imamura M, Kato F, Nakayama T, Ohara O, Yamashita M	dependent airway inflammation through selective modulation of chromatin status at the Il5 gene locus.	PLoS One	16(8)	e61785	2013
Shirasaki Y, Yamagishi M, Shimura N, Hijikata A, Ohara O.	Toward an understanding of immune cell sociology: real-time monitoring of cytokine secretion at the single-cell level.	IUBMB Life	65(1)	28-34	2013
Oshima K, Nagase T, Imai K, Nonoyama S, Obara M, Mizukami T, Nunoi H, Kanegane H, Kuribayashi F, Amemiya S, Ohara O.	A Dual Reporter Splicing Assay Using HaloTag-containing Proteins.	Curr Chem Genomics	6	27-37	2012
Takezaki S, Yamada M, Kato M, Park MJ, Maruyama K, Yamazaki Y, Chida N, Ohara O, Kobayashi I, Ariga T.	Chronic mucocutaneous candidiasis caused by a gain-of-function mutation in the STAT1 DNA-binding domain.	J Immunol.	189(3)	1521-1526	2012
Mohammadzadeh I, Yeganeh M, Aghamohammadi A, Parvaneh N, Behniafard N, Abolhassani H, Tabassomi F, Hemmat M, Kanegane H, Miyawaki T, Ohara O, Rezaei N.	Severe primary antibody deficiency due to a novel mutation of mu heavy chain.	J Investig Allergol Clin Immunol	22(1)	78-79	2012
Nonaka F, Migita K, Haramura T, Sumiyoshi R, Kawakami A, Eguchi K.	Colchicine-responsive protracted gouty arthritis with systemic inflammatory reactions.	Mod Rheumatol.		in press	
Nakamura T, Migita K, Ando Y, Takaoka H, Suzushima H, Shiraishi N.	Amyloid A amyloidosis in a Japanese patient with familial Mediterranean fever associated with homozygosity for the pyrin variant M694I/M694I.	Mod Rheumatol.		in press	
Fujikawa K, Migita K, Tsukada T, Umeda M, Nonaka F, Kawakami A, Eguchi K.	Interleukin-6 targeting therapy in familial Mediterranean fever.	Clin Exp Rheumatol.	31(3 Suppl 77)	150-1	2013
Mori S, Yonemura K, Migita K.	Familial Mediterranean Fever Occurring in an Elderly Japanese Woman with Recent-onset Rheumatoid Arthritis.	Intern Med.	52(3)	385-388	2013
Ishiguro T, Takayanagi N, Kobayashi K, Migita K, Yanagisawa T, Hoshi T, Sugita Y.	Magnetic resonance imaging can detect thoracic inflammation due to familial Mediterranean fever.	Mod Rheumatol.	23(3)	604-7	2013
Eguchi M, Miyashita T, Shirouzu H, Sato S, Izumi Y, Takeoka A, Ohno T, Sumiyoshi R, Nishino A, Jiuchi Y, Nonaka F, Eguchi K, Kawakami A, Migita K	Coexistence of polymyositis and familial Mediterranean fever.	Mod Rheumatol.	23(2)	374-8	2013
Washio M, Nakano T, Kawaguchi Y, Takagi K, Kiyohara C, Tsukamoto H, Tokunaga S, Horiuchi T	Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in Japan: a review of the literature.	Mod. Rheumatol.	23(2)	210-217	2013
Marsh RA, Rao K, Satwani P, Lehmberg K, Müller I, Li D, Kim MO, Fischer A, Latour S, Sedlacek P, Barlogis V, Hamamoto K, Kanegane H, Milanovich S, Margolis DA, Dimmock D, Casper J, Douglas DN, Amrolia PJ, Veys P, Kumar AR, Jordan MB, Bleesing JJ, Filipovich AH	Allogeneic hematopoietic cell transplantation for XIAP deficiency: an international survey reveals poor outcomes.	Blood	121(6)	877-83	2013
Inoue Y, Kawaguchi Y, Shimojo N, Yamaguchi K, Morita Y, Nakano T, Arima T, Tomiita M, Kohno Y	A case of infantile Takayasu arteritis with a D382E NOD2 mutation: an unusual phenotype of Blau syndrome/early-onset sarcoidosis.	Mod Rheumatol	23	837-839	2013
Ota Y, Kawaguchi Y, Takagi K, Ichida H, Gono T, Hanaoka M, Higuchi T, Yamanaka H	Ghrelin attenuates collagen production in lesional fibroblasts from patients with systemic sclerosis.	Clin Immunol	147	71-78	2013
Katsumata Y, Kawaguchi Y, Baba S, Hattori S, Tahara K, Ito K, Iwasaki T, Yamaguchi N, Hattori H, Nagata K, Okamoto Y, Yamanaka H, Hara M	Serum antibodies against the 70k polypeptides of the U1 ribonucleoprotein complex are associated with psychiatric syndromes in systemic lupus erythematosus: a retrospective study.	Mod Rheumatol	23	71-80	2013
Hanaoka M, Gono T, Kawaguchi Y, Uchida K, Koseki Y, Katsumata Y, Kaneko H, Takagi K, Ichida H, Nitta K, Yamanaka H	Urinary free light chain is a potential biomarker for ISN/RPS class III/IV lupus nephritis.	Rheumatology	52	2149-2157	2013
Terao C, Ohmura K, Kawaguchi Y, Nishimoto T, Kawasaki A, Takehara K, Furukawa H, Kochi Y, Ota Y, Ikari K, Sato S, Tohma S, Yamada R, Yamamoto K, Kubo M, Yamanaka H, Kuwana M, Tsuchiya N, Matsuda F, Mimori T	PLD4 as a novel susceptibility gene for systemic sclerosis in a Japanese population.	Arthritis Rheum	65	472-480	2013
Suzuki T, Ikari K, Kawaguchi Y, Yano K, Iwamoto T, Kawamoto M, Toyama Y, Taniguchi A, Yamanaka H, Momohara S	Non-synonymous variant (Gly307Ser) in CD226 is associated with susceptibility in Japanese rheumatoid arthritis patients.	Mod Rheumatol	23	200-202	2013

雑誌（和文）

発表者名	論文タイトル名	発表雑誌	巻号	ページ	出版年
内尾寛子、額田貴之、井庭憲人、深尾大輔、橋本有紀子、田部有香、井上美保子、濱畑啓悟、吉田晃、百井亨、河合朋樹、西小森隆太、平家俊男	NEMO蛋白異常をフローサイトメトリーにより早期診断した色素失調症の新生児例	日本小児科学会雑誌	117巻8号	1303-7	2013
河合朋樹、平家俊男	メンデル遺伝型マイコバクテリア感染症	臨床免疫・アレルギー科	60巻5号	548-52	2013
阿部純也、西小森隆太、平家俊男	Aicardi-Goutieres症候群	アレルギー・免疫	20巻10号	62-69	2013
河合朋樹、平家俊男	患者レジストリーと遺伝子診断	アレルギー・免疫	20巻10号	14-23	2013
横田俊平, 西小森隆太, 高田英俊, 菊地雅子, 野澤智, 金高太一, 木澤敏毅, 宮前多佳子, 森雅亮, 平家俊男, 原寿郎, 今川智之	クリオピリン関連周期性発熱症候群に対する生物学的製剤治療の手引き(2012) カナキヌマブ(総説)	日本小児科学会雑誌	116巻9号	1337-1341	2012
西小森隆太, 井澤和司, 平家俊男	【クローズアップ感染症】PFAPA以外の周期性発熱症候群についての知見(解説/特集)	小児内科	44巻7号	1221-1226	2012
西小森隆太, 井澤和司, 平家俊男	原発性免疫不全症における臨床遺伝学 日本における自己炎症疾患の遺伝子診断について(解説)	日本遺伝カウンセリング学会誌	33巻1号	63-68	2012
西小森隆太, 平家俊男	自己炎症症候群	小児内科	44巻増刊号	290-291	2012
斎藤潤、中畑龍俊	疾患特異的iPS細胞	再生医療	Vol.12 No.1	19-32	2013
戸田尚子、原　寿郎	2.疾患と栄養　先天性免疫不全症と低栄養	臨床栄養		印刷中	2014
原　寿郎	2.幹細胞異常と内科系疾患、現状と展望　1)造血幹細胞の異常:先天性免疫不全症	日本内科学会雑誌	102(9)	2255-61	2013
原　寿郎	小児感染・免疫疾患の発症におけるヒトー環境相互作用	小児感染免疫	25(1)	41-53	2013
原　寿郎	シリーズ小児医療第6回　原発性免疫不全症研究:最新の進歩	あいみっく	.34(3)	50-5	2013
原　寿郎	<Clinical Science> 自然免疫が関与する炎症性疾患:川崎病	炎症と免疫	21(6)	62-7	2013
原　寿郎	こどもの発熱の原因とその対処法	ふたば	77	18-24	2013
原　寿郎	原発性免疫不全症(PID)ー悪性腫瘍, 血液疾患を合併するPIDを中心にー	日本小児血液・がん学会雑誌	49(3)	237-241	2012
高田英俊、大賀正一、原　寿郎	自己炎症症候群. 特集　知っておきたい最新の免疫不全症候群分類ー診断から治療までー	小児科診療	76(3)	印刷中	2012
横田俊平	炎症性疾患の理解と治療の進歩(解説)	日本病院総合診療医学会雑誌	4巻1号	8-10	2013
大西秀典, 寺本貴英, 久保田一生, 近藤直実	皮膚症状からみた自己炎症性症候群	小児科	53	1201-1209	2012
右田清志、野中文陽、和泉泰衛、江口勝美、中村正、井田弘明、上松一永	家族性地中海熱の臨床	炎症と免疫	21	40-6	2013
川上純、右田清志、井田弘明	自己炎症疾患	medicina	50	458-62	2013
井田弘明	遺伝性発熱性疾患の遺伝子診断ガイドライン	リウマチ科	50	507-511	2013
井田弘明	自己炎症症候群	最新医学	68	2561-2569	2013
井田弘明、有馬和彦、金澤伸雄、吉浦孝一郎	中條-西村症候群の原因遺伝子とプロテアソーム機能異常	リウマチ科	47(6)	654-660	2012
井田弘明、福田孝昭	自己炎症症候群の定義と分類	九州リウマチ	32(2)	75-78	2012
井田弘明、福田孝昭	自己炎症症候群	日本臨床	70(suppl 8)	561-568	2012
井田弘明	自己炎症症候群	日本医事新報	4615	78-83	2012
井田弘明、有馬和彦、金澤伸雄、吉浦孝一郎	プロテアソーム病	炎症と免疫	20(6)	609-614	2012
有馬和彦、井田弘明、金澤伸雄、吉浦孝一郎	プロテアソームの機能阻害型遺伝子変異が新規自己炎症疾患である中條ー西村症候群を引き起こす	細胞工学	31	68-69	2012
中野倫代, 神戸直智	Blau症候群／若年発症サルコイドーシス研究の現状と展望	日本臨床	71	737-41	2013
江原瑞枝, 神戸直智	序 ～自己炎症症候群の概説と現在提唱されている定義・分類～	アレルギー・免疫	20	1395-8	2013
神戸直智	皮膚から診断する全身疾患　皮膚所見から考える自己炎症症候群	日皮会誌	123	2826-8	2013
神戸直智, 中村悠美	連載「自己炎症症候群の多様性」 CAPSでみられるヒスタミン非依存性蕁麻疹	炎症と免疫	20	183-188	2012
神戸直智	特集「蕁麻疹患者のQOL向上術」 蕁麻疹様皮疹を呈するクリオピリン関連周期性症候群の診断と管理.	Monthly Book Derma デルマ	194	63-69	2012
神戸直智, 中村悠美	特集「アナフィラキシーショック」 NLRP3インフラマソームを介したマスト細胞の活性化	臨床免疫・アレルギー科	58	560-564	2012
神戸直智	自己炎症症候群と皮膚疾患の関連　ー治りにくい蕁麻疹(それと乾癬)についてー	日皮会誌	122	3286-3288	2012
荻野篤彦、金澤伸雄、古江増隆	皮膚を編むー小児掌蹠丘疹性皮膚炎（砂かぶれ様皮膚炎）や自己炎症性症候群の臨床と病態	ラジオNIKKEI マルホ皮膚科セミナー特別番組「明日の治療指針」		印刷中	
金澤伸雄	中條ー西村症候群：和歌山発・プロテアソーム不全による新しい自己炎症疾患	日本臨床皮膚科医会近畿ブロック会誌		印刷中	
金澤伸雄	中條 - 西村症候群	分子リウマチ治療	7	25-29	2014
金澤伸雄	サルコイドーシス	Monthly Book Derma「肉芽腫のすべて」	204	15-23	2013
金澤伸雄	日本で見出された自己炎症疾患ー中條ー西村症候群ー	皮膚アレルギー・接触皮膚炎学会雑誌	7	158-168	2013

金澤伸雄	中條・西村症候群	アレルギー・免疫	20	1456-1462	2013
金澤伸雄	NOD2関連疾患	炎症と免疫	20	517-522	2012
金澤伸雄	皮膚—紅斑など皮膚症状から診断へ	小児内科	44	85-89	2012
上松一永	【小児疾患の診断治療基準(第4版)】(第2部)疾患　生体防御・免疫不全　重症複合免疫不全症	小児内科	44(11)	224-225	2012
森尾友宏	好中球過剰活性化制御機構と炎症	炎症と免疫	21	345-351	2013
森尾友宏	先天性免疫不全症の病態と思春期以降のマネジメント	血液内科	65	599-607	2012
森尾友宏	【クローズアップ感染症】 <感染性疾患の基礎的な知見の進歩・概念の変化>感染症と自然免疫	小児内科	44	959-965	2012
森尾友宏	【サイトカインのすべて(完全改訂版)】 サイトカイン投与およびサイトカイン抑制による治療 免疫不全症	臨床免疫・アレルギー科	57	838-844	2012
森尾友宏	原発性免疫不全症における臨床遺伝学 T細胞系免疫異常症における遺伝子診療	日本遺伝カウンセリング	33	49-53	2012
森尾友宏	分類不能型免疫不全症	日本臨牀	70	2011-2021	2012
森尾友宏	分類不能型免疫不全症 Update	日本臨床免疫	35	14-22	2012
武井修治	自然免疫と適応免疫のクロストーク～SLEにおける自然免疫の機能不全	臨床とウイルス		印刷中	2014
武井修治	若年発症サルコイドーシス/Blau症候群	アレルギー・免疫	30	1438-1446	2013
右田清志, 和泉泰衛, 野中文陽, 江口勝美	日本人における自己炎症疾患関連遺伝子の異常.　特集 <Basic Science>　リウマチ・膠原病のゲノム解析 update.	炎症と免疫.	21(5)	401-409	2013
右田清志, 和泉泰衛, 野中文陽, 江口勝美	遺伝性自己炎症疾患－家族性地中海熱－. I. 炎症の諸相.	別冊BIO Clinica.	2(2)	52-57	2013
右田清志, 和泉泰衛, 野中文陽, 江口勝美	痛風. Clinical Science　自然免疫が関与する炎症性疾患.	炎症と免疫	21(6)	517-524	2013
右田清志	リウマチ性疾患とIL-1阻害療法. 臨床リウマチ医のための基礎講座.	臨床リウマチ.	25(4)	299-301	2013
江口勝美, 野中文陽, 右田清志	自己炎症疾患の新たな展開－内科医でも知っておく必要がありますー.	アレルギー	62(8)	942-949	2013
上田尚靖、塚本浩、堀内孝彦	TRAPSの病態と病因	炎症と免疫	20巻3号	293-298	2012
今井耕輔	原発性免疫不全症の最新国際分類	アレルギー科	58	446-466	2012
今井耕輔	自然免疫について	チャイルドヘルス	16	608-613	2013

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EXTENDED REPORT

Somatic *NLRP3* mosaicism in Muckle-Wells syndrome. A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes

Kenji Nakagawa,[1] Eva Gonzalez-Roca,[2] Alejandro Souto,[3] Toshinao Kawai,[4] Hiroaki Umebayashi,[5] Josep María Campistol,[6] Jeronima Cañellas,[7] Syuji Takei,[8] Norimoto Kobayashi,[9] Jose Luis Callejas-Rubio,[10] Norberto Ortego-Centeno,[10] Estíbaliz Ruiz-Ortiz,[2] Fina Rius,[2] Jordi Anton,[11] Estibaliz Iglesias,[11] Santiago Jimenez-Treviño,[12] Carmen Vargas,[13] Julian Fernandez-Martin,[14] Inmaculada Calvo,[15] José Hernández-Rodríguez,[16] María Mendez,[17] María Teresa Dordal,[18] Maria Basagaña,[19] Segundo Bujan,[20] Masato Yashiro,[21] Tetsuo Kubota,[22] Ryuji Koike,[22] Naoko Akuta,[23] Kumiko Shimoyama,[24] Naomi Iwata,[25] Megumu K Saito,[26] Osamu Ohara,[27] Naotomo Kambe,[28] Takahiro Yasumi,[1] Kazushi Izawa,[1] Tomoki Kawai,[1] Toshio Heike,[1] Jordi Yagüe,[2] Ryuta Nishikomori,[1] Juan I Aróstegui[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Juan I Aróstegui, Immunology Department (esc 4-pl 0), Hospital Clínic, Villarroel, 170, Barcelona 08036, Spain; jiaroste@clinic.ub.es and Dr Ryuta Nishikomori, Department of Pediatrics, Kyoto University Graduate School of Medicine, 54 Shogoin Sakyo, Kyoto 606-8507, Japan; rnishiko@kuhp.kyoto-u.ac.jp

KN, EG-R, RN and JIA contributed equally.

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ABSTRACT

Familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome are dominantly inherited autoinflammatory diseases associated to *gain-of-function NLRP3* mutations and included in the cryopyrin-associated periodic syndromes (CAPS). A variable degree of somatic *NLRP3* mosaicism has been detected in ≈35% of patients with CINCA. However, no data are currently available regarding the relevance of this mechanism in other CAPS phenotypes.

Objective To evaluate somatic *NLRP3* mosaicism as the disease-causing mechanism in patients with clinical CAPS phenotypes other than CINCA and *NLRP3* mutation-negative.

Methods *NLRP3* analyses were performed by Sanger sequencing and by massively parallel sequencing. Apoptosis-associated Speck-like protein containing a CARD (ASC)-dependent nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) activation and transfection-induced THP-1 cell death assays determined the functional consequences of the detected variants.

Results A variable degree (5.5–34.9%) of somatic *NLRP3* mosaicism was detected in 12.5% of enrolled patients, all of them with a MWS phenotype. Six different missense variants, three novel (p.D303A, p.K355T and p.L411F), were identified. Bioinformatics and functional analyses confirmed that they were disease-causing, *gain-of-function NLRP3* mutations. All patients treated with anti-interleukin1 drugs showed long-lasting positive responses.

Conclusions We herein show somatic *NLRP3* mosaicism underlying MWS, probably representing a shared genetic mechanism in CAPS not restricted to CINCA syndrome. The data here described allowed definitive diagnoses of these patients, which had serious implications for gaining access to anti-interleukin 1 treatments under legal indication and for genetic counselling. The detection of somatic mosaicism is difficult when using conventional methods. Potential candidates should benefit from the use of modern genetic tools.

Cryopyrin-associated periodic syndromes (CAPS) are a group of autoinflammatory diseases that include familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome, also known as neonatal-onset multisystem inflammatory disease (NOMID).[1] Some clinical features are shared by almost all CAPS phenotypes (ie, onset during childhood, an urticaria-like skin rash) whereas others are restricted to certain phenotypes (ie, serum amyloid A protein (AA) amyloidosis in MWS, destructive arthropathy in CINCA-NOMID).[1] CAPS are caused by dominantly inherited or de novo *NLRP3* mutations.[2–4] This gene encodes for cryopyrin, a component of one of the cytosolic complexes named inflammasomes that generate the active form of interleukin 1ß (IL-1ß).[5] Previous studies showed a *gain-of-function* behaviour for those *NLRP3* mutations associated with CAPS because they provoke an uncontrolled IL-1ß overproduction, representing the basis from which to treat these patients with anti-IL-1 drugs.[3 6] Genetic heterogeneity was suggested in CINCA-NOMID because only ≈55% of patients was *NLRP3* mutation-positive.[3 4] The use of novel genetic methods recently detected somatic *NLRP3* mosaicism in ≈35% of patients with CINCA-NOMID.[7 8] However, no data are currently available about the role of this genetic mechanism in other CAPS phenotypes because genetic heterogeneity has hitherto been scarcely reported in previous studies.

We herein show the causal role of somatic *NLRP3* mosaicism in patients with MWS, in whom previous studies did not detect *NLRP3* mutations, suggesting that this genetic mechanism is shared among the different CAPS phenotypes.

PATIENTS AND METHODS

Patients

For this study we enrolled patients with a clinical suspicion of CAPS, with a phenotype of MWS and overlapping syndromes, and *NLRP3* mutation-negative in previous studies. The clinical inclusion criteria were the presence of an urticaria-like skin rash and at least one of the following symptoms: recurrent fever, recurrent arthritis, recurrent aseptic meningitis, sensorineural deafness or AA amyloidosis (see online supplementary table S1 for details). All patients with a CINCA-NOMID phenotype were excluded. The patients' data were collected by direct interviews and chart reviews. Written informed consent from patients (or patients' parents if younger than 18-years-old) was obtained at each institution. The ethics committees of Hospital Clinic, Barcelona and the Graduate School of Medicine, Kyoto University approved this study, which was conducted in accordance with the Helsinki Declaration.

NLRP3 analyses

These analyses were performed in the Graduate School of Medicine, Kyoto University or in the Hospital Clínic, Barcelona. Genomic DNA was obtained from whole peripheral blood using QIAmp DNA Blood Mini Kit (QIAgen, Germany). For Sanger sequencing all exons of *NLRP3* gene were amplified by PCR using the primers and conditions previously described.[2] The PCR amplicons were purified with Illustra ExoStar 1-Step kit (GE Healthcare, USA), bidirectional fluorescence sequencing using ABI BigDye Terminator V.3.1 Cycle Sequencing Kit (Applied Biosystems, USA) and run on an automated ABI 3730XL DNA analyzer. For massively parallel DNA sequencing, all exons of *NLRP3* gene were amplified as previously described.[8] Library preparation and emulsion PCR were performed according to manufacturer's instructions. All sequencing runs were performed on the GS Junior 454 Sequencer using the GS Junior Titanium Sequencing kits (Roche, Switzerland). The obtained sequences were analysed using the Amplicon Variant Analyzer software.

Bioinformatics analyses

In silico sequence analyses were performed using two different algorithms. The Sorting Intolerant from Tolerant is a sequence homology based tool that predicts whether the amino acid substitution is or is not probably damaging by reporting a score. The PolyPhen-2 is a tool for prediction of the possible impact of an amino acid substitution on the structure and function of a protein, and qualitatively appraised as benign, possibly damaging or probably damaging.[9 10]

Functional studies

The functional consequences of the novel *NLRP3* variants were evaluated in two in vitro assays.[11] Wild type and mutant *NLRP3* cDNA, obtained by mutagenesis PCR, were subcloned into the expression vectors pEF-BOSEX and pcDNA5/TO (Invitrogen, USA). The Apoptosis-associated Speck-like protein containing a CARD (ASC)-dependent nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB) activation was evaluated using a dual-luciferase reporter assay in HEK293FT cells transfected with *NLRP3*-pEF-BOSEX plasmids with a NF-kB reporter construct (pNF-kB-luc, BD Biosciences) and an internal control construct (pRLTK, Toyo Ink) in the presence or absence of ASC-expression plasmid. To evaluate the necrosis-like cell death, the THP-1 cell line (a human monocytic cell line derived from a patient with acute monocytic leukemia) was transfected with green fluorescent protein (GFP)-tagged *NLRP3*-pcDNA5/TO plasmids. After 4 h, cells were stained with 7-aminoactinomycin D and cell death of GFP positive cell was analysed by FACS Caliber (Becton-Dickinson).

Statistical analyses

Continuous variables are presented as the mean±SD or as the median and IQR, while categorical variables are presented as numbers, ratios and/or percentages. To detect potential differences among patients with germline mutations and with somatic mutations, the Mann-Whitney U test was used for continuous variables and Fisher's exact test was used for categorical variables.

RESULTS

Genetic analyses

Fifty-six patients (23 Japanese and 33 Spanish) who fulfilled the inclusion criteria were enrolled. Sanger sequencing of the *NLRP3* gene did not identify mutations in any patients. However, small peaks with reduced signal intensities compared with controls were detected in two patients: the A-to-C transversion at c.908 position in Patient 1 and the A-to-G transition at c.1000 position in Patient 2, which encode for the p.Asp303Ala and p.Ile334Val cryopyrin variants, respectively (figure 1A and table 1). Massively parallel DNA sequencing was performed in all patients and revealed somatic *NLRP3* mosaicism in seven patients (7/56; 12.5%). Six different nucleotide changes, all of them located in the exon 3, were detected, and their frequency varied notably among patients, ranging from 5.5% to 34.9% (table 1). All *NLRP3* variants encode for non-synonymous amino acid changes, three of them being novel (p.Asp303Ala, p.Lys355Thr and p.Leu411Phe) and the remainder already described (p.Ile334Val, p.Phe523Leu and p.Glu567Lys) (figure 1B). In Patient 4 the frequency of the mutated *NLRP3* allele remained identical in blood samples obtained over an 8-year period (table 1).

Bioinformatics and functional analyses

All missense *NLRP3* variants were predicted to be possibly or probably damaging to cryopyrin structure and/or function according to at least one of the two algorithms employed, with the only exception of p.Glu567Lys variant (table 1). Interestingly, this *NLRP3* variant was twice detected in the unrelated patients with somatic mosaicism, and has also been reported in other patients with CAPS, reasonably supporting its pathogenic effect.[7 11] We did not find any of the detected *NLRP3* variants in two groups of ethnically matched healthy individuals (Japanese controls n: 200 chromosomes; Spanish controls n: 500 chromosomes) nor in the database National Center for Biotechnology Information (NCBI) single nucleotide polymorphism database (dbSNP) Build 137 (table 1), reasonably ruling out that they could be rare gene polymorphisms.

Finally we evaluated their functional consequences by two different in vitro assays. The results showed that all *NLRP3* variants induced ASC-dependent NF-κB activation (figure 1C) and necrosis-like programmed cell death of THP-1 cell line (figure 1D) at a similar or higher level than those induced by other well-known disease-causing mutations (p.Arg260Trp, p.Asp303Asn and p.Tyr570Cys). Altogether, these data clearly support a pathogenic effect for all *NLRP3* mutations detected as somatic mutations in the enrolled patients.

Clinical features of patients with somatic *NLRP3* mosaicism

At the time of inclusion in the study, the clinical diagnosis of patients with somatic *NLRP3* mosaicism was compatible with MWS. Neither consanguinity nor familial history of the disease

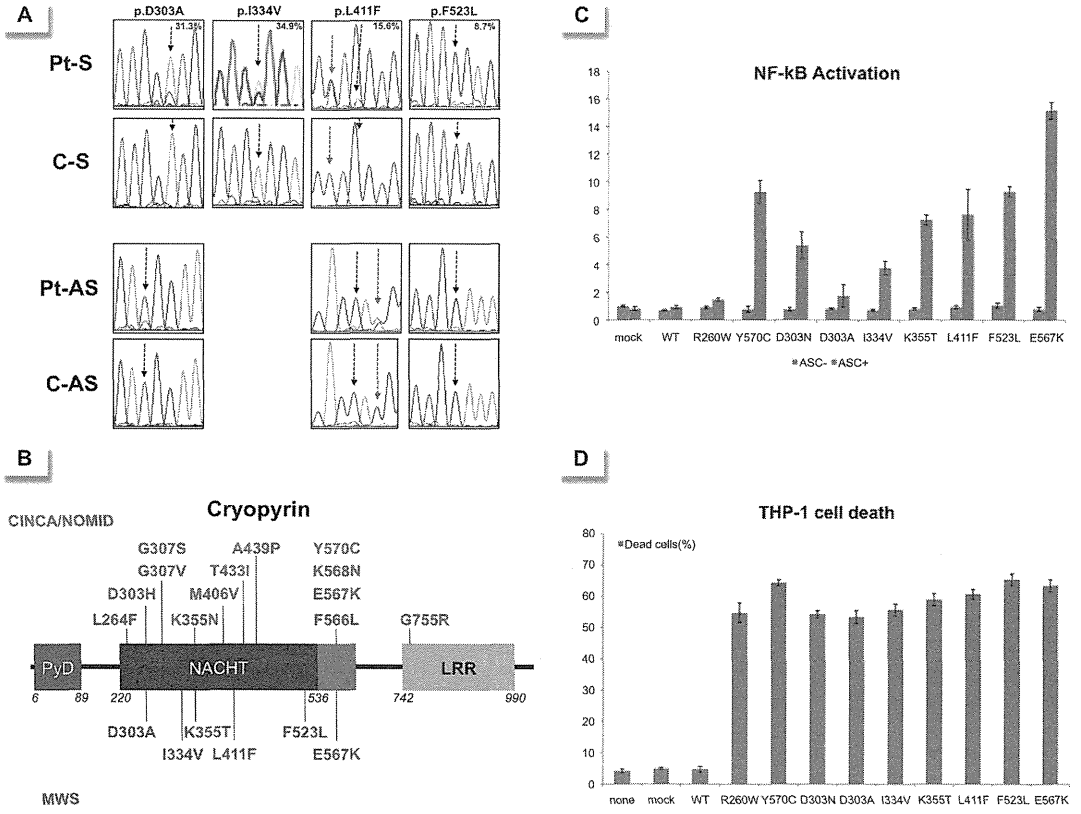

Figure 1 (A) Sense (upper rows) and antisense (bottom rows) chromatograms from four patients with somatic *NLRP3* mosaicism and controls obtained by Sanger sequencing using genomic DNA extracted from whole blood. The black arrows show the *NLRP3* positions where the somatic mutations were detected. The percentage in the upper panels represents the frequency of the mosaicism obtained by massively parallel DNA sequencing in each patient. The red arrows indicate the c.1231 C>T *NLRP3* polymorphism (rs#148478875). (B) Structural organisation of cryopyrin. Above the protein structure are indicated all missense cryopyrin variants that have been detected as somatic mutations in patients with chronic, infantile, neurological, cutaneous and articular (CINCA)-neonatal-onset multisystem inflammatory disease (NOMID) in previous reports, and those below the protein structure are the missense variants detected as somatic mutations in the present study. (C) ASC-dependent NF-kB activation and (D) necrotic THP-1 cell death, induced by the detected *NLRP3* mutations. Values are the mean±SD of triplicate experiments, and data are representative of two independent experiments. AS, antisense; ASC, Apoptosis-associated Speck-like protein containing a CARD; C, control; LRR, leucine-rich repeat; mock, vector without *NLRP3*; MWS, Muckle-Wells syndrome; NACHT, a family of NTPases that originally included the NAIP, CIITA, HETE-E and TP-1 proteins; NF-kB, nuclear factor kappa-light chain-enhancer of activated B cells; None, nothing transfected; Pt, patient; PyD, pyrin domain; S, sense; WT, wild type *NLRP3*.

was reported in any of them. The inflammatory disease started during their infancy or childhood (median: 4 years; IQR: 1.3–9.0 years), with an urticaria-like skin rash and a marked inflammatory acute response as the main features at that time (see table 2 for clinical details at the disease onset).

All patients referred to the chronic course of their disease, with variable disease evolution (median: 20 years; IQR: 12–26 years). During this time, recurrent arthritis (6/7; 85.7%), headache (5/7; 71.4%) and recurrent conjunctivitis (4/7; 57.1%) mainly added to those features detected at the disease onset. None of these patients developed AA amyloidosis, whereas five of them (71.4%) developed progressive bilateral sensorineural deafness (see table 3 for a detailed summary of clinical features detected during the course of the disease).

Outcome of anti-IL-1 blockade

Five patients with somatic *NLRP3* mosaicism were treated with anti-IL-1 drugs. Only Patient 5 was treated with anakinra (100 mg/24 h subcutaneous for a duration of 20 months). Three patients only received canakinumab: Patient 2 (150 mg/8 weeks subcutaneous for a duration of 13 months), Patient 3 (2 mg/kg/8 weeks subcutaneous for a duration of 16 months) and Patient 6 (initial dose of 150 mg/4 weeks, subsequently increased up to 300 mg/4 weeks, for a duration of 14 months). Patient 7 was first treated with anakinra (1 mg/kg/24 h subcutaneous for a duration of 24 months) and subsequently switched to canakinumab (150 mg/8 weeks subcutaneous for a duration of 14 months). All patients showed a marked and sustained improvement while treated with anti-IL-1 drugs, with a complete remission of urticaria-like skin rash (5/5), fever (3/3), conjunctivitis (2/2) and aseptic meningitis (1/1), and marked benefits for arthritis (complete response in 75%) and headache (complete response in 75%, and marked improvement in 25%). Inversely, IL-1 blockade did not improve the sensorineural deafness (0/4). The clinical improvement was associated with sustained reductions of erythrocyte sedimentation rate and C reactive protein level, and normalisation of white blood cell, neutrophil and platelets counts, and haemoglobin level (see figure 2 for details).

Comparative phenotype analyses

To identify potential clinical differences among patients with germline or with somatic *NLRP3* mutations two cohorts of

Table 1 Summary of genetic data of patients with somatic *NLRP3* mosaicism

Pt (Country)	Phenotype	Massively parallel DNA sequencing: Nucleotide exchange*	Amino acid exchange	Mutated allele frequency	Coverage	Bioinformatics analyses: SIFT	PolyPhen-2	Population genetics†	Reference	Analysed relatives: Kinship	Results
1 (Spain)	MWS	c.908 A>C	p.D303A	31.3%‡	622×‡	Damaging	Probably damaging	Absent	Present Study	n.d.	n.d.
2 (Japan)	MWS	c.1000 A>G	p.I334V	34.9%‡	1060×‡	Damaging	Benign	Absent	12	Father	Negative§
										Mother	Negative§
3 (Japan)	MWS	c.1064 A>C	p.K355T	20.2%‡	100×‡	Tolerated	Probably damaging	Absent	Present Study	n.d.	n.d.
4¶ (Spain)	MWS	c.[1231 C>T; 1233 G>T]	p.L411F	14.4%‡	590×‡	Tolerated	Possibly damaging	Absent	Present Study	Mother	Negative§
4** (Spain)	MWS	c.[1231 C>T; 1233 G>T]	p.L411F	15.6%‡	870×‡	Tolerated	Possibly damaging	Absent	Present Study	Mother	Negative§
5 (Spain)	MWS	c.1569 C>A	p.F523L	8.7%††	569×††	Tolerated	Possibly damaging	Absent	3	Daughter	Negative§
6 (Japan)	MWS	c.1699 G>A	p.E567K	5.6%‡	1211×‡	Tolerated	Benign	Absent	11	n.d.	n.d.
7 (Japan)	MWS	c.1699 G>A	p.E567K	5.5%‡	724×‡	Tolerated	Benign	Absent	11	n.d.	n.d.

*NCBI Reference Sequence NM_001243133.1.
†Data of population genetics obtained from NCBI dbSNP Build 137.
‡Mean of two independent experiments.
§Analyses performed by Sanger sequencing.
¶Blood sample collected in 2002.
**Blood sample collected in 2009.
††Mean of four independent experiments.
MWS, Muckle-Wells syndrome; n.d., not done; Pt, patient; SIFT, Sorting Intolerant from Tolerant.

patients with MWS were compared. The group of patients with MWS with somatic *NLRP3* mosaicism included the seven patients described here whereas the cohort of patients with MWS with germline mutations included 41 patients (13 Japanese and 28 Spanish) from our databases. In this last group the germline status was established by means of pedigree analyses and/or by massively parallel sequencing. As expected, the familial history of the disease was a significant variable between the two groups. No significant differences were detected among the main clinical features (fever, urticaria-like rash, joint, neurological and ocular involvements, and deafness) despite their variable frequency in each group (see table 4 for details). However, patients with somatic *NLRP3* mosaicism seemed to have late onsets of the disease and of the sensorineural deafness, an increased incidence of arthritis and a reduced risk of developing AA amyloidosis, when compared with patients with germline mutations.

DISCUSSION

CINCA-NOMID syndrome represents the severest CAPS phenotype, and is usually a consequence of de novo *NLRP3* mutations. Recent works have established its genetic basis, with ≈55% of patients carrying germline *NLRP3* mutations and ≈35% carrying somatic *NLRP3* mosaicism.[3–4 7 11–16] However, no studies addressing the presence of somatic *NLRP3* mosaicism have been undertaken in other CAPS phenotypes because genetic heterogeneity has been poorly described in them, with only five reported patients with *NLRP3* mutation-negative MWS.[17–19] This scenario prompted us to hypothesise that somatic *NLRP3* mosaicism might be an underlying genetic mechanism in patients with other CAPS phenotypes. For this proposal two ethnically different cohorts of candidates were screened, and 12.5% of them (7/56) carried variable degree of somatic *NLRP3* mosaicism in peripheral blood. Additional evidences, as shown here, definitively support that the detected *NLRP3* variants are pathogenic

Table 2 Summary of clinical features of patients with somatic *NLRP3* mosaicism at the onset of the disease

Pt	Age at disease onset	Cold-exposure trigger	Urticaria-like skin rash	Fever	Joint involvement	CNS involvement	Acute inflammatory response*	First diagnoses
1	18 years	–	Yes	Yes	Arthralgias	–	Yes	
2	2 years	–	Yes	–	Arthralgias	–	Yes	JIA
3	1 week	–	Yes	–	–	–	Yes	Chronic urticaria, So-JIA
4	14 years	–	Yes	Yes	–	–	Yes	Erythema nodosa
5	4 years	Yes	Yes	Yes	Arthralgias	–	Yes	
6	4 years	Yes	Yes	Yes†	Oligoarthritis	–	Yes	Oligo-JIA
7	7 months	-	Yes	Yes	Oligoarthritis	–	n.a.	So-JIA, TRAPS

*Defined by increased values of white blood cells (normal range 4.00–11.00×10^3/dL), circulating neutrophils (normal range 45–75%), platelets (normal range 130–400×10^3/dL), C reactive protein (normal range <1 mg/dL) and/or erythrocyte sedimentation rate (normal <10 mm/h).
†Low-grade fever.
–, absent; CNS, central nervous system; JIA, juvenile idiopathic arthritis; n.a., not available; Pt, Patient; So-JIA, systemic-onset juvenile idiopathic arthritis; TRAPS, TNF receptor-associated periodic syndrome.

Table 3 Summary of clinical manifestations detected in patients with somatic *NLRP3* mosaicism during the course of the disease

Pt	Sex (Age)	Cold-exposure trigger	Urticaria-like skin rash	Joint involvement					CNS involvement			Deafness (age at onset)	Ocular involvement	AA amyloidosis
				Fever	Type of arthritis	Involved joints	Symmetric	Erosive	Arthropathy	Headache	Aseptic meningitis	Papilloedema			
1	M (39 years)	–	Yes	Yes	Polyarthritis	Large and small	–	–	–	–	–	–	Yes (38 years)	Conjunctivitis	–
2	M (14 years)	–	Yes	–	–	–	–	–	–	Yes	Yes	–	Yes (7 years)	–	–
3	F (12 years)	–	Yes	–	Monoarthritis	Large	–	–	–	Yes	–	–	Yes (6 years)	–	–
4	F (41 years)	–	Yes	Yes	Polyarthritis	Small	–	–	–	Yes	–	–	–	Conjunctivitis	–
5	M (64 years)	Yes*	Yes	Yes†	Polyarthritis	Large and small	–	–	–	–	–	–	Yes (45 years)	–	–
6	F (16 years)	Yes†	Yes	Yes	Oligoarthritis	Large	–	–	–	Yes	–	–	–	Conjunctivitis	–
7	M (16 years)	–	Yes	Yes	Oligoarthritis	Large	–	–	–	Yes	–	–	Yes (13 years)	Conjunctivitis	–

*Always.
†Occasionally.
–, No or absent; AA, serum amyloid A protein; CNS, central nervous system; F, female; M, male; Pt, Patient.

and include their absence in panels of ethnically matched controls and in a database of genomic diversity, in silico analyses that predict their damaging effect for the function and/or structure of cryopyrin, and in vitro functional studies that clearly showed its *gain-of-function* behaviour. Taken together these evidences support that somatic *NLRP3* mosaicism is a genetic mechanism shared by different CAPS phenotypes, and it is not restricted to CINCA-NOMID syndrome.

Among *NLRP3* mutations detected 50% (3/6) were novel, representing an unexpected high proportion for a small cohort. Taking into account their consequences on the cryopyrin function it is conceivable to hypothesise that, in germline status, they could be incompatible with life. We have also found a marked variability in the degree of somatic mosaicism among patients, which may have important consequences. For diagnostic purposes the level of somatic mosaicism could be the determining factor in achieving a definitive genetic diagnosis. Those patients with mosaicism around, or higher than, 15% will probably be detected in conventional studies using Sanger's method by means of careful analyses, as we have shown in the patients' chromatograms. However, those patients with frequencies of less than 15% are probably missed by Sanger sequencing and will only be detected by using new technologies that are not currently widely available. The differences of disease severity observed among patients with somatic mosaicism, including those from this study and those from previous reports, could be explained by different and cumulative factors, which probably cannot be independently analysed. These factors might include, at least, the type of amino acid exchange, its location in the cryopyrin, its functional consequence in the normal cryopyrin function, and the degree and tissue distribution of somatic mosaicism. We must also note that all known somatic *NLRP3* mutations seem to be located in some few amino acid residues (303, 355, 567) or in small regions of cryopyrin (303–307, 433–439 and 566–570), probably representing hot spots for these types of mutations. Consequently these regions should be carefully analysed when using Sanger sequencing to identify potential carriers of somatic mosaicism.

All patients with somatic *NLRP3* mosaicism were sporadic patients, with no affected relatives, which is notably different from patients with germline mutations (positive familial history in 65.9%). Their main clinical features were compatible with a MWS phenotype and similar to those previously described in patients with germline mutations, with the potential exceptions of a reduced incidence of AA amyloidosis, an increased incidence of recurrent arthritis, and slightly older ages at the disease onset and also at onset of sensorineural deafness. It is interesting to note that most patients (4/7; 57.1%) were misdiagnosed as having juvenile idiopathic arthritis when the disease started, a similar misdiagnosis previously reported in different inherited autoinflammatory diseases.[20–23] Despite the evidence shown here, the actual frequency of somatic *NLRP3* mosaicism is unknown and probably underestimated. In our study a potential bias in the selection of patients could exist because they were selected on the basis of the presence of an urticaria-like skin rash associated with other symptoms. Recent studies have described atypical CAPS presentations in patients with germline *NLRP3* mutations in whom urticaria-like skin rash was nearly absent.[24 25] These data suggest that clinical diversity of CAPS is probably wider than previously described and further studies are necessary to delineate the profile of potential candidates to carry somatic *NLRP3* mosaicism.

The evidence obtained may have serious implications for patients, especially with regards to treatment and genetic

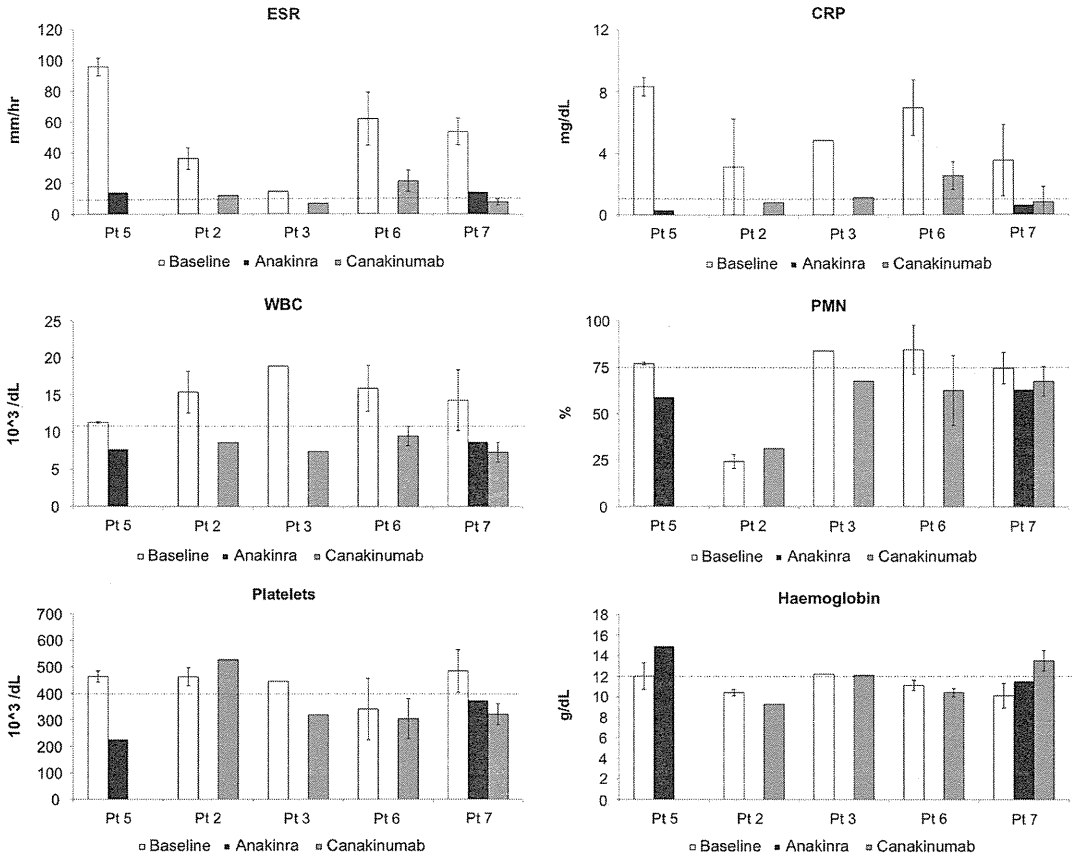

Figure 2 Laboratory values obtained in the five patients treated with different anti-interleukin 1 drugs. Patient's graphics were ordered as follows: First, those graphics from the patient who only received treatment with anakinra (Pt 5), followed by those from patients who only received treatment with canakinumab (Pt 2, 3 and 6) and finally those from the patient who received both treatments (Pt 7). Vertical bars represent the mean±SD of values obtained during treatment periods. Horizontal discontinued lines represent the upper limit of the normal range, with the only exception of the haemoglobin box, in which this line represents the lower limit of the normal range. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; PMN, polymorphonuclears; WBC, white blood cell count.

Table 4 Comparison of main clinical data of patients carrying germline versus somatic *NLRP3* mutations

Clinical features	Patients with germline *NLRP3* mutations (n:41)	Patients with somatic *NLRP3* mutations (n:7)	p Value
Age at disease onset (years)—median (IQR)	0.5 (0.0–4.4)	4.0 (1.3–9.0)	n.s. (p=0.223)
Delay of diagnosis (years)—median (IQR)	33.0 (10–49)	20 (12–26)	n.s. (p=0.416)
Presence of familial history of the disease (%)	65.9	0	p=0.002
Cold exposure as disease triggering factor (%)	36.6	28.6	n.s. (p=1.000)
Fever (%)	63.4	71.4	n.s. (p=1.000)
Urticaria-like skin rash (%)	87.8	100	n.s. (p=1.000)
Joint involvement			
Arthralgias (%)	80.5	85.7	n.s. (p=1.000)
Arthritis (%)	53.7	85.7	n.s. (p=0.214)
Neurological involvement			
Headache (%)	56.1	71.4	n.s. (p=0.683)
Aseptic meningitis (%)	29.3	14.3	n.s. (p=0.656)
Papilloedema (%)	12.2	0	n.s. (p=1.000)
Ocular involvement			
Conjunctivitis (%)	61.0	57.1	n.s. (p=1.000)
Uveitis (%)	17.1	0	n.s. (p=0.573)
Sensorineural deafness (%)	68.3	71.4	n.s. (p=1.000)
Age at onset of deafness (years)—median (IQR)	7.0 (5.5–11)	13.0 (7–38)	n.s. (p=0.210)
AA amyloidosis (%)	17.1	0	n.s. (p=0.573)

Patients with germline mutations were carriers of one of the next *NLRP3* mutations: p.R170S (c.508 C>A), p.R260W (c.778 C>T), p.V262A (c.785 T>C), p.D303N (c.907 G>A), p.H312P (c.935 A>C), p.T348M (c.1043 C>T), p.A439T (c.1315 G>A), p.A439V (c.1316 C>T), p.F443L (c.1329 C>G), p.E567A (c.1700 A>C) and p.Y859C (c.2576 A>G).
AA, serum amyloid A protein; n.s., not significant differences.

counselling. The outcome of IL-1 blockade in patients with somatic *NLRP3* mosaicism was nearly identical to those reported in patients with germline mutations.[26 27] The only symptom that did not improve with IL-1 blockade was the sensorineural deafness. In this regard, apparently contradictory responses have been reported, with improvement or amelioration in some patients and no response in others.[14 17 28–30] It has been suggested that the time of evolution of deafness previous to starting anti-IL-1 drugs could be a determining factor for the type of response, but probably additional and unknown factors could also play a role in this particular manifestation. We have also observed a notable delay in gaining access to anti-IL-1 drugs with respect to the disease onset (median: 20 years; IQR: 12–26 years), because these treatments were administered under legal indication once the definitive CAPS diagnosis was established by means of the identification of somatic *NLRP3* mosaicism. Taking into account the excellent response observed to IL-1 blockade, it is reasonable to hypothesise that if this was started earlier it should have provoked the non-appearance of some severe complications such as deafness.

For an appropriate genetic counselling the scenario is extremely different in patients with CAPS with germline or with somatic mutations. In the case of germline mutations, the risk of transmission to future pregnancies is 50%. Inversely, the prediction of the risk of transmission in cases of somatic mosaicism is more complex, because it may vary in the different tissues, it is not usually determined in gonadal tissues, and its detection probably requires new sensitive genetic methods that are not widely available. The vertical transmission of a somatic mutation is an extremely rare event, with only one case recently described in MWS.[31] Consequently, this possibility should be considered during the genetic counselling of these patients, although one of the main messages to patients is that its probability remains low.

We show that somatic *NLRP3* mosaicism underlies MWS and is probably a shared genetic mechanism in different CAPS phenotypes, and not restricted to CINCA/NOMID syndrome. Its detection was achieved by using massively parallel sequencing, and functional studies confirmed the *gain-of-function* behaviour of the detected variants. The detection of somatic mosaicism has had serious clinical implications for patients, including access to treatment under legal indication, adequate follow-up and ensuring appropriate genetic counselling. Further studies are necessary to delineate the clinical phenotype of candidates to looking for somatic mosaicism, in which new sensitive genetic technologies should be used.

Author affiliations
[1]Department of Pediatrics, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[2]Department of Immunology-CDB, Hospital Clínic-IDIBAPS, Barcelona, Spain
[3]Department of Rheumatology, Hospital Universitario de Santiago de Compostela, Santiago de Compostela, Spain
[4]Department of Human Genetics, National Center for Child Health and Development, Tokyo, Japan
[5]Department of General Pediatrics, Miyagi Children's Hospital, Sendai, Japan
[6]Department of Nephrology, Hospital Clínic-IDIBAPS, Barcelona, Spain
[7]Department of Rheumatology, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[8]Faculty of Medicine, School of Health Sciences, Kagoshima University, Kagoshima, Japan
[9]Department of Pediatrics, School of Medicine, Shinshu University, Matsumoto, Japan
[10]Department of Internal Medicine, Hospital Universitario San Cecilio, Granada, Spain
[11]Department of Pediatric Rheumatology, Hospital Sant Joan de Deu, Esplugues, Spain
[12]Department of Pediatrics, Hospital Central de Asturias, Oviedo, Spain
[13]Department of Rheumatology, Hospital Virgen de la Macarena, Sevilla, Spain
[14]Department of Internal Medicine, Hospital Meixoeiro, Vigo, Spain
[15]Department of Pediatric Rheumatology, Hospital Universitario La Fe, Valencia, Spain
[16]Department of Autoimmune Diseases, Hospital Clínic-IDIBAPS, Barcelona, Spain
[17]Department of Pediatrics, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[18]Department of Allergy, Hospital Municipal de Badalona, Badalona, Spain
[19]Allergy Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain
[20]Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain
[21]Department of Pediatrics, Okayama University Graduate School of Medicine, Okayama, Japan
[22]Department of Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan
[23]Department of Pediatrics, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
[24]Third Internal Medicine Department, Hamamatsu University School of Medicine, Hamamatsu, Japan
[25]Department of Infection and Immunology, Aichi Children's Health and Medical Centre, Obu, Japan
[26]Department of Clinical Application, Center for iPS cell research and application, Kyoto University, Kyoto, Japan
[27]Department of Human Genome Research, Kazusa DNA Research Institute, Kisarazu, Japan
[28]Department of Dermatology, Chiba University Graduate School of Medicine, Chiba, Japan

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REFERENCES

1 Kastner DL, Brydges S, Hull KM. Chapter 27: Periodic fever syndromes. In: Ochs HD, Smith CI Edvard, Puck JM. eds. *Primary immunodeficiency diseases. A molecular and genetic approach*. 2nd edn. Oxford University Press, 2007:367–89.
2 Hoffman HM, Mueller JL, Broide DH, *et al*. Mutations of a new gene encoding a putative pyrin-like protein causes familial cold autoinflamatory syndrome and Muckle-Wells syndrome. *Nature Genet* 2001;29:301–5.
3 Aksentijevich I, Nowak M, Mallah M, *et al*. De novo CIAS1 mutations, cytokine activation, and evidence of genetic heterogeneity in patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID). *Arthritis Rheum* 2002;46:3340–8.
4 Feldman J, Prieur AM, Quartier P, *et al*. Chronic Infantile Neurological Cutaneous and Articular Syndrome is Caused by mutations in CIAS1, a Gene Highly Expressed in polymorphonuclear Cells and Chondrocytes. *Am J Hum Genet* 2002;71:198–203.
5 Martinon F, Mayor A, Tschopp J. The inflammasomes: guardians of the body. *Annu Rev Immunol* 2009;27:229–65.
6 Agostini L, Martinon F, Burns K, *et al*. NALP3 forms an IL-1β-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. *Immunity* 2004;20:319–25.
7 Tanaka N, Izawa K, Saito MK, *et al*. High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome. Results of an International multicenter collaborative study. *Arthritis Rheum* 2011;63:3625–32.
8 Izawa K, Hijikata A, Tanaka N, *et al*. Detection of base substitution-type somatic mosaicism of the NLRP3 gene with >99.9% statistical confidence by massively parallel sequencing. *DNA Res* 2012;19:143–52.
9 Ng PC, Henikoff S. Accounting for human polymorphisms predicted to affect function. *Genome Res* 2002;12:436–46.
10 Ramensky V, Bork P, Sunyaev S. Human non-synonymous SNPs: server and survey. *Nucleic Acids Res* 2002;30:3894–900.

11 Saito M, Nishikomori R, Kambe N, *et al*. Disease-associated CIAS1 mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients. *Blood* 2008;111:2132–41.
12 Cuisset L, Jeru I, Dumont B, *et al*. French CAPS study group. Mutations in the autoinflammatory cryopyrin-associated periodic syndrome gene: epidemiological study and lessons from eight years of genetic analysis in France. *Ann Rheum Dis* 2011;70:495–9.
13 Arostegui JI, Lopez Saldaña MD, Pascal M, *et al*. A somatic NLRP3 Mutation as a cause of a Sporadic Case of CINCA/NOMID Syndrome. Novel evidences of the role of low-level mosaicism as pathophysiological mechanism underlying Mendelian inherited diseases. *Arthritis Rheum* 2010;62:1158–66.
14 Neven B, Marvillet I, Terrada C, *et al*. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with Neonatal-Onset Multisystem Inflammatory Disease/Chronic Infantile Neurologic, Cutaneous, Articular syndrome. *Arthritis Rheum* 2010;62:258–67.
15 Aróstegui JI, Aldea AI, Modesto C, *et al*. Clinical and genetic heterogeneity among Spanish patients with recurrent autoinflammatory syndromes-associated to CIAS1/PYPAF1/NALP3 gene. *Arthritis Rheum* 2004;50:4045–50.
16 Saito M, Fujisawa A, Nishikomori R, *et al*. Somatic mosaicism of CIAS1 in a patient with Chronic Infantile Neurologic, Cutaneous, Articular syndrome. *Arthritis Rheum* 2005;52:3579–85.
17 Rynne M, Maclean C, Bybee A, *et al*. Hearing improvement in a patient with variant Muckle-Wells syndrome in response to interleukin 1 receptor antagonism. *Ann Rheum Dis* 2006;65:533–4.
18 Kagami S, Saeki H, Kuwano Y, *et al*. A probable case of Muckle-Wells syndrome. *J Dermatol* 2006;33:118–21.
19 Aksentijevich I, Putnam CD, Remmers EF, *et al*. The clinical continuum of cryopyrinopathies. Novel CIAS1 Mutations in North American patients and a new cryopyrin model. *Arthritis Rheum* 2007;56:1273–85.
20 Ohnishi H, Teramoto T, Iwata H, *et al*. Characterization of NLRP3 variants in Japanese cryopyrin-associated periodic syndrome patients. *J Clin Immunol* 2012;32:221–9.
21 Wise CA, Bennett LB, Pascual V, *et al*. Localization of a gene for familial recurrent arthritis. *Arthritis Rheum* 2000;43:2041–5.
22 Kanazawa N, Okafuji I, Kambe N, *et al*. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. *Blood* 2005;105:1195–7.
23 Aróstegui JI, Arnal C, Merino R, *et al*. NOD2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. *Arthritis Rheum* 2007;56:3805–13.
24 Verma D, Eriksson P, Sahdo B, *et al*. Two adult siblings with atypical cryopyrin-associated periodic syndrome due to a novel M299V mutation in NLRP3. *Arthritis Rheum* 2010;62:2138–43.
25 Murphy G, Daly M, O'Sullivan M, *et al*. An unusual phenotype in Muckle-Wells syndrome associated with NLRP3 E311K. *Rheumatology* 2011;50:419–20.
26 Hawkins PN, Lachmann HJ, Aganna E, *et al*. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;50:607–12.
27 Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, *et al*. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med* 2009;360:2416–25.
28 Mirault T, Launay D, Cuisset L, *et al*. Recovery from deafness in a patient with Muckle-Wells syndrome treated with anakinra. *Arthritis Rheum* 2006;54:1697–700.
29 Kuemmerle-Deschner JB, Tyrrell PN, Koetter I, *et al*. Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome. *Arthritis Rheum* 2011;63:840–9.
30 Weegerink NJ, Schraders M, Leijendeckers J, *et al*. Audiometric characteristics of a Dutch family with Muckle-Wells syndrome. *Hear Res* 2011;282:243–51.
31 Jiménez-Treviño S, González-Roca E, Ruiz-Ortiz E, *et al*. First report of vertical transmission of a somatic *NLRP3* mutation in cryopyrin-associated periodic syndromes. *Ann Rheum Dis* 2013;72:1109–10.

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Somatic *NLRP3* mosaicism in Muckle-Wells syndrome. A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes

Kenji Nakagawa, Eva Gonzalez-Roca, Alejandro Souto, et al.

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